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FORM PTO-1390 (REV 10-96) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: IU33CIP-3PCT/US

U.S. APPLICATION NO. (If known, see 37 CFR 1.5):

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US96/15712	30 September 1996 (30.09.96)	29 September 1995 (29.09.95)

TITLE OF INVENTION: METHODS FOR ENHANCED VIRUS-MEDIATED DNA TRANSFER USING MOLECULES WITH VIRUS- AND CELL-BINDING DOMAINS

APPLICANT(S) FOR DO/EO/US: WILLIAMS, David A.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). unsigned
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter
16. ☒ Other items or information:
    a. Request
    b. International Publication
    c. Response to Invitation to Correct Defects
    d. Demand for Intnl Prelim Examination
    e. PCT/IB/332
    f. Response to Written Opinion
    g. International Preliminary Examination Report
    h. PCT/IB/304
    i. PCT/IB/308

"Express Mail" label number EM566459008US

Date of Deposit 27 MARCH 1998

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37CFR § 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Linda C. Shelby

Signature of person mailing paper or fee

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
	PCT/US96/15712	IU3361P-3PCT/US

17. ☒ The following fees are submitted:

	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Search Report has been prepared by the EPO or JPO $910.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) ..... 720. ~~$700.00~~		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $770.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $1040.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 720.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE		
Total claims	22	- 20 =	2	X $22.00	$ 44.00	
Independent claims	4	- 3 =	1	X ~~$80.00~~ 82	$ 82	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ $260.00	$	
TOTAL OF ABOVE CALCULATIONS =					$ 846.00	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).					$	
SUBTOTAL =					$ 846.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +					$	
TOTAL NATIONAL FEE =					$ 846.-	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +					$	
TOTAL FEES ENCLOSED =					$ 846.-	
					Amount to be: refunded	$
					charged	$

a. ☒ A check in the amount of $ 846.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-3030. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

Kenneth A. Gandy
WOODARD, EMHARDT, NAUGHTON, MORIARTY & MCNETT
Bank One Center/Tower, Suite 3700
111 Monument Circle
Indianapolis, Indiana 46204 US

Kenneth A. Gandy
SIGNATURE

Kenneth A. Gandy
NAME

#33,386
REGISTRATION NUMBER

PCT INTERNATIONAL APPLIC[ON] TRANSMITTAL LETTER	30 September 1996
REGARDING THE INTERNATIONAL APPLICATION OF INDIANA UNIVERSITY FOUNDATION	DOCKET OR REFERENCE NUMBER IU33CIP-3PCT

ENTITLED
ETHODS FOR ENHANCED VIRUS-MEDIATED DNA TRANSFER USING MOLECULES WITH VIRUS- AND CELL- BINDING DOMAINS

Certification under 37 CFR 1.10 (if applicable)

TB861770503US — "Express Mail" mailing number

30 September 1996 — Date of Deposit

I hereby certify that this application is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Linda C. SHELBY — (Typed or printed name of person mailing application)

Linda C. Shelby — (Signature of person mailing application)

To the United States Receiving Office (RO/US):

Accompanying this transmittal letter is the above-identified International application, including a completed Request form (PCT/RO/101). Please process the application according to the provisions of the Patent Cooperation Treaty.

The following requests are made of the RO/US:

1. [X] PREPARATION AND TRANSMITTAL OF CERTIFIED COPY OF PRIORITY DOCUMENTS—Please prepare and transmit to the International Bureau a certified copy of the United States origin priority documents identified in Box VI of the Request form (37 CFR 1.451).

   To cover the cost of copy preparation and certification (37 CFR 1.19(a)(3) and (b)(1)),
   - [X] a (check) (money order) in the amount of $ 30.00 included in fee is attached to this transmittal letter.
   - [ ] the RO/US is hereby authorized to charge the following deposit account no.: _____.

2. [X] CHOICE OF INTERNATIONAL SEARCHING AUTHORITY—It is requested that the International Search be performed by the following International Searching Authority:
   - [X] United States Patent and Trademark Office (ISA/US)
   - [ ] European Patent Office (ISA/EP)

   The appropriate Search fee for the above-named Authority is indicated on the Fee Calculation Sheet (PCT/RO/101 Annex).

3. [X] SUPPLEMENTAL SEARCH FEES (ONLY WHEN ISA/US CONDUCTS THE INTERNATIONAL SEARCH.)—Please charge any Supplemental Search fees that may be required by the United States International Searching Authority (ISA/US) to deposit account no.: 23-3030.

   I understand that this authorization is subject to my oral confirmation thereof in each instance and that it in no way limits my right to submit a protest against payment of the Supplemental Search fees, but is merely an administrative aid to assure that the ISA/US may timely complete the Search Report.

NOTE: SUPPLEMENTAL SEARCH FEES FOR ISA/EP ARE PAYABLE DIRECTLY TO THE EUROPEAN PATENT OFFICE

4. [X] DISCLOSURE INFORMATION—In order to assist in screening the accompanying International application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied:

   A. [ ] There is no prior filed application relating to this invention. (29.09.95)

   B. [X] There is a prior application, serial number 08/536,891 filed on 29 September 1995 which contains subject matter that is 60/024,169 19 August 1996 (19.08.96)

   60/024,169 1. [XX] substantially identical to that of the accompanying International application.

   08/536,891 2. [XX] less than that of the accompanying International application. The additional subject matter of the International application appears on pages(s) and line(s) throughout the applicatior

   3. [ ] more than that of the accompanying International application.

   C. [ ] Disclosure information cannot be covered by the language of Points 4A or 4B above due to the involvement of several prior applications or for other reasons. A separate sheet on which the disclosure information is explained is attached to this transmittal letter.

5. [ ] REQUEST FOR FOREIGN TRANSMITTAL LICENSE—According to the provisions of 35 U.S.C. 184 and 37 CFR 5.11, a license to transmit the accompanying International application to foreign agencies or international authorities is hereby requested.

SIGNER IS THE	NAME OF SIGNER (Typed)
[ ] APPLICANT [ ] COMMON REPRESENTATIVE [X] (ATTORNEY) (AGENT) REG NO 33,386	Kenneth A. GANDY SIGNATURE Kenneth A. Gandy

PCT

FEE CALCULATION SHEET

Annex to the Request

For Receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: IU33CIP-3 PCT

Applicant: INDIANA UNIVERSITY FOUNDATION

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . 220 [T]

2. SEARCH FEE . . . . . 430 [S]

International search to be carried out by US

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 94 sheets.

first 30 sheets . . . . . 677 [b_1]

64 (remaining sheets) x 13 (additional amount) = 832 [b_2]

Add amounts entered at b_1 and b_2 and enter total at B . . . . 1509 [B]

Designation Fees

The international application contains 45 designations.

45 (number of designation fees payable *(maximum 11)*) x 164 (amount of designation fee) = 1804 [D]

Add amounts entered at B and D and enter total at I . . . . . 3313 [I]

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT . . . . . 30 [P]

5. TOTAL FEES PAYABLE

Add amounts entered at T, S, I and P, and enter total in the TOTAL box . . $ 3,993 TOTAL

[ ] The designation fees are not paid at this time.

MODE OF PAYMENT

- [X] authorization to charge deposit account (see below)
- [ ] bank draft
- [ ] coupons
- [X] cheque
- [ ] cash
- [ ] other *(specify)*:
- [ ] postal money order
- [ ] revenue stamps

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ US

- [ ] is hereby authorized to charge the total fees indicated above to my deposit account.
- [X] is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.
- [ ] is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

23-3030 (Deposit Account Number)

30 Sept 1996 (Date *(day/month/year)*)

Kenneth A. Gandy (Signature Kenneth A. GANDY 33,386)

Form PCT/RO/101 (Annex) (January 1996)

See Notes to the fee calculation sheet

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For Receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* IU33CIP-3PCT

Box No. I TITLE OF INVENTION

METHODS FOR ENHANCED VIRUS-MEDIATED DNA TRANSFER USING MOLECULES WITH VIRUS- AND CELL-BINDING DOMAINS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

INDIANA UNIVERSITY FOUNDATION
P.O. Box 500
Showalter House
Bloomington, Indiana 47404
United States of America

☐ This person is also inventor.

Telephone No. 812-855-8311

Facsimile No.

Teleprinter No.

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WILLIAMS, David A.
8751 N. Moore Road
Indianapolis, Indiana 46278
United States of America

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GANDY, Kenneth A.
WOODARD, EMHARDT, NAUGHTON, MORIARTY & MCNETT
Bank One Center/Tower, Suite 3700
111 Monument Circle
Indianapolis, Indiana 46204 US

SEE CONTINUATION TO BOX NO. IV ON SHEET NO. 3

Telephone No. 317-634-3456

Facsimile No. 317-637-7561

Teleprinter No. 810-341-3283

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead t indicate a special address to which correspondence should be sent.

Box No.V . DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- [X] AP **ARIPO Patent:** KE Kenya, LS Lesoth , MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] EP **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- [X] AL Albania
- [ ] AM Armenia
- [ ] AT Austria
- [X] AU Australia
- [ ] AZ Azerbaijan
- [X] BB Barbados
- [X] BG Bulgaria
- [X] BR Brazil
- [ ] BY Belarus
- [X] CA Canada
- [ ] CH and LI Switzerland and Liechtenstein
- [X] CN China
- [X] CZ Czech Republic
- [ ] DE Germany
- [ ] DK Denmark
- [X] EE Estonia
- [ ] ES Spain
- [ ] FI Finland
- [ ] GB United Kingdom
- [X] GE Georgia
- [X] HU Hungary
- [X] IL Israel
- [X] IS Iceland
- [X] JP Japan
- [ ] KE Kenya
- [ ] KG Kyrgyzstan
- [X] KP Democratic People's Republic of Korea
- [X] KR Republic of Korea
- [ ] KZ Kazakstan
- [X] LK Sri Lanka
- [X] LR Liberia
- [ ] LS Lesotho
- [X] LT Lithuania
- [ ] LU Luxembourg
- [X] LV Latvia
- [ ] MD Republic of Moldova
- [X] MG Madagascar
- [X] MK The former Yugoslav Republic of Macedonia
- [X] MN Mongolia
- [ ] MW Malawi
- [X] MX Mexico
- [X] NO Norway
- [X] NZ New Zealand
- [X] PL Poland
- [ ] PT Portugal
- [X] RO Romania
- [X] RU Russian Federation
- [ ] SD Sudan
- [ ] SE Sweden
- [X] SG Singapore
- [X] SI Slovenia
- [X] SK Slovakia
- [ ] TJ Tajikistan
- [ ] TM Turkmenistan
- [XX] TR Turkey
- [XX] TT Trinidad and Tobago
- [X] UA Ukraine
- [ ] UG Uganda
- [X] US United States of America
  CONTINUATION-IN-PART/CONTINUATION
- [XX] UZ Uzbekistan
- [XX] VN Viet Nam

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- [X] CU Cuba
- [X] LC Saint Lucia
- [X] BA Bosnia & Herzegovina

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of _____

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet need not be included in the request.*

Use this box in the following cases:

1. If, in any of the Boxes, the space is insufficient to furnish all the information:	*in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient;*
in particular:	
(i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available:	*in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III;*
(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked:	*in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*
(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America:	*in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*
(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents:	*in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*
(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "Continuation" or "Continuation-in-part":	*in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*
(vi) if there are more than three earlier applications whose priority is claimed:	*in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*
2. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty:	*in such case, write "Statement Concerning Non-Prejudicial Disclosures or Exceptions to Lack of Novelty" and furnish that statement below.*

Continuation to Box No. IV Agent

WOODARD, Harold R.; EMHARDT, C. David; NAUGHTON, Joseph A., Jr.; MORIARTY, John V.; McNETT, John C.; HENRY, Thomas Q.; DURLACHER, James M.; REEVES, Charles R.; WAGNER, Vincent O.; ZLATOS, Steve; BEREVESKOS, Spiro; BAHRET, William F.; BROWNING, Clifford W.; FRISK, R. Randall; LUEDERS, Daniel J.; BECK, Michael D.; GANDY, Kenneth A.; THOMAS, Timothy N.; SISSELMAN, Kerry P.; JONES, Kurt N.; ALLIE, John H.; MICHAEL, Jeffrey A.; KNOLL, Deborah R.; BANTA, Holiday W.; COLE, Troy J.; PAYNTER, L. Scott; JOHNSTON, Lisa H. and ROWE, James L., all of Woodard, Emhardt, Naughton, Moriarty & McNett, Bank One Center/Tower, Suite 3700, 111 Monument Circle, Indianapolis, Indiana 46204 United States of America

Continuation to Box No. V DESIGNATION OF STATES

Continuation-in-part: United States Application No. 08/536,891 filed 29 September 1995 (29.09.95) and
Continuation of : United States Application No. 60/024,169 filed 19 August 1996 (19.08.96)

Box No. VI PRIORITY CL Further priority claims indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
item (1) US	29 September 1995 (29.09.95)	08/536,891	
item (2) US	(19.08.96) 19 August 1996	60/024,169 (per postcard)	
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): (1) and (2)

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA / US

Earlier search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:*

Country (or regional Office):	Date (day/month/year):	Number:
US	29 September 1995 (29.09.95)	08/536,891
US	19 August 1996 (19.08.96)	60/024,169

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	: 4	sheets
2. description	: 58	sheets
3. claims	: 4	sheets
4. abstract	: 1	sheets
5. drawings	: 27	sheets
Total	: 94	sheets

This international application is accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney
2. ☒ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☐ priority document(s) *identified in Box No. VI as item(s):*
5. ☒ fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☐ nucleotide and/or amino acid sequence listing (diskette)
8. ☒ other *(specify):* Transmittal Letter (dup)

Figure No. 20 of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Applicant:

INDIANA UNIVERSITY FOUNDATION

Agent: Kenneth A. Gandy

(Kenneth A. Gandy)

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority specified by the applicant: ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For Receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* IU33CIP-3PCT

Box No. I TITLE OF INVENTION

METHODS FOR ENHANCED VIRUS-MEDIATED DNA TRANSFER USING MOLECULES WITH VIRUS- AND CELL-BINDING DOMAINS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

INDIANA UNIVERSITY FOUNDATION
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Bloomington, Indiana 47402
United States of America

☐ This person is also inventor.

Telephone No.: 812-855-8311

Facsimile No.:

Teleprinter No.:

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WILLIAMS, David A.
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Indianapolis, Indiana 46278
United States of America

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GANDY, Kenneth A.
WOODARD, EMHARDT, NAUGHTON, MORIARTY & MCNETT
Bank One Center/Tower, Suite 3700
111 Monument Circle
Indianapolis, Indiana 46204 US

SEE CONTINUATION TO BOX NO. IV ON SHEET NO. 3

Telephone No.: 317-634-3456

Facsimile No.: 317-637-7561

Teleprinter No.: 810-341-3283

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PCT application of:	
INDIANA UNIVERSITY FOUNDATION	Authorized Officer
	D. Nguyen
International Application No. PCT/US96/15712	Mailing Date 13 October, 1997
International Filing Date 30 September, 1996	
METHODS FOR ENHANCED VIRUS-MEDIATED DNA TRANSFER USING MOLECULES WITH VIRUS- AND CELL-BINDING DOMAINS	Agent's File Reference IU33CIP-3PCT

RESPONSE TO FIRST WRITTEN OPINION

Hon. Commissioner of Patents and Trademarks
Box PCT
Washington, D. C. 20231
Sir:

In response to the first Written Opinion mailed 12 August 1997, Applicant submits herewith new pages 59-64 to substitute for current pages 59-63, and the following remarks in support of this application. New pages 59-63 contain a new claim set, in which claims 1, 3, 5, 6 and 10 have been amended, claims 11, 12 and 15 have been cancelled, and claims 16-25 have been added to more particularly point out and distinctly claim the invention. New page 64 contains the same abstract as original page 63.

REMARKS

Claims 1-10, 13-14 and 16-25 remain pending in the present application. A positive indication has been given as to the industrial applicability of claims 1-15, as to the novelty

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Signature of person mailing paper or fee

of claims 1-2 and 6-15, and as to the inventive step of claim 14. These positive indications are acknowledged with appreciation.

Negative indications have been given as to the novelty of claims 3-5, and as to the inventive step of claims 1-13 and 15. To the extent applied to claims 11-12 and 15, these indications are mooted by the cancellation of these claims. To the extent that these indications are maintained as to the remaining claims, as discussed in detail below, it is believed that these indications are in error because claims 3-5 distinguish from the Moritz *et al.* reference relied upon, and because claims 1-10, 13 and 16-25 each embody an inventive step over the combination of Moritz *et al.* in view of Haraguchi *et al.*. Accordingly, it is submitted that the International Preliminary Examination Report should give positive indications in all regards as to all pending claims.

As indicated above, the Written Opinion states that claims 3-5 as originally presented lack novelty over the Moritz *et al.* article. In support of this position, the Written Opinion argues that absent evidence to the contrary, "the composition and the method of Moritz *et al.* have the properties cited in the claims." The attention of the authorized officer is directed to claims 3-5, which in each instance require that the relevant cellular population be essentially free from the polycationic agent (e.g. polybrene, as used by Moritz *et al.*) and contain the claimed ligand-containing material(s). To the contrary, Moritz *et al.* expressly teach the use of the polycationic agent, polybrene. As such, the position that claims 3-5 lack novelty over Moritz *et al.* cannot properly be maintained, and its withdrawal in favor of a corresponding positive indication is solicited.

The Written Opinion also takes the position that claims 1-10 and 13 lack inventive step over the combination of the Moritz *et al.* and Haraguchi *et al.* references. These indications are also believed to be incorrect, for the following reasons.

A feature of the invention is the discovery that the conduct of viral infection protocols in the absence of polycationic agents such as polybrene, but in the presence of material including a ligand which binds the targeted cells and a ligand which binds the retrovirus, as claimed, provides substantially improved levels of transduction of the cells. For example, the attention of the authorized officer is directed to Example 15 of the specification

(beginning at page 53) and accompanying Figures 19 and 20. The reported experiments analyzed the level of transduction of cells using varying concentrations of the polycationic agent, polybrene. As the Example reports:

> As shown in Figure 19, the number of G418 resistant NIH/3T3 colonies decreases dramatically with increasing Polybrene concentrations, ranging from about 14 when no Polybrene was used down to about 4 when 12.5 μg/ml Polybrene was used. Similarly, Figure 20 reflects that nearly 40 colonies were observed when the protocol was conducted in the absence of Polybrene, whereas the corresponding value when using 10 μg/ml was less than 15.

Thus, the transduction efficiency with NIH/3T3 cells *more than tripled* when no polybrene was used as compared to 12.5 μg/ml polybrene (Figure 19), and with clonogenic bone marrow cells it *more than doubled* when no polybrene was used as compared to 10 μg/ml polybrene (Figure 20). There is absolutely nothing in the Moritz *et al.* and Haraguchi *et al.* references, alone or combined, which teaches, suggests or motivates such claimed protocols or gives any hint of the unexpected, large improvements in transduction efficiency which are thereby obtained. Yet, those very unexpected advantages address needs which the cited and other references admit to -- increasing transduction efficiency while at the same time decreasing concerns of toxicity. Accordingly, it is clear that the present claims are patentably distinguished from this combination of references, and a proper analysis reveals that the current rejection cannot properly be maintained.

Discussing the references now in more detail, the Moritz *et al.* reference is relied upon for teaching the use of fibronectin in effecting gene transfer into hematopoietic cells, and subsequent transplantation therapy. Haraguchi *et al.* is relied upon for teaching that polybrene "has an inhibiting effect on infection with a retrovirus". From this combination, the Action asserts that the claimed invention is obvious "given the Moritz *et al.* reference disclosing the negative limitation of polybrene's usage in a retroviral infection protocol". This latter statement is not understood, since Moritz *et al.* utilize polybrene and teach nothing as to a "negative limitation" of its usage. Moreover, the Haraguchi *et al.* abstract presents no data, reports mixed results, and in fact concludes that "polycations had no marked effects on infection with human retroviruses ..." in their work. It is thus difficult if

not impossible to reach any relevant conclusions from Haraguchi *et al.* This, combined with the persistence of polybrene use in retroviral protocols in the field, minimizes or eliminates the relevance of the Haraguchi *et al.* In fact, to the extent that the Haraguchi *et al.* reference is relevant, its report of "no marked effects" of polycations makes the marked increases in transduction efficiency achieved be the present invention all the more surprising.

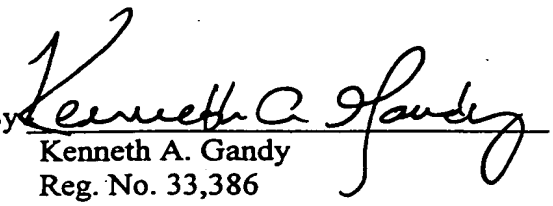
It is therefore respectfully submitted that there is lacking in these references, alone or combined, any teaching of the present invention protocols which are conducted in the presence of the claimed material and in the absence of the polycationic agent, so as to increase transduction efficiency. Moritz *et al.* did not and could not teach such surprising results, as all of their experiments employed polybrene. Haraguchi *et al.* did not and could not teach such a surprising result, as their experiments did not use the claimed material.

Moreover, the comments in the Written Opinion regarding polybrene's non-approved status, and other references in the literature further support the patentability of the present invention. Illustratively, Anderson *et al.* (copy enclosed) state at page 194 that "When considering retroviral-mediated gene transfer as a means of treating genetic diseases, the safety as well as the efficacy of the proposed procedure must be considered ... Potential risks should be minimized and current guidelines for the preparation of biologic materials should be used whenever possible." Anderson *et al.* propose substituting one polycationic agent shown to have toxicity (protamine sulfate) for another (polybrene), whereas the present invention enables the elimination of such toxic agents while nonetheless achieving high transduction efficiency. Thus, the literature evidences the fact that skilled artisans continued to search for ways to improve transduction efficiency, and were looking to other polycationic agents similar to polybrene rather than to eliminating the use of such polycationic agents in combination with using the claimed material, as in the present invention. Accordingly, when properly considered as a whole, the inventions embodied in claims 1-10, 13 and 16-25 do indeed possess an inventive step over the cited references.

In summary, in light of the foregoing remarks, it is believed that each of claims 1-10, 13-14, and 16-25, is novel and embodies an inventive step over the cited references. The

establishment of an International Preliminary Examination Report which is positive in all respects as to these claims is therefore solicited.

Respectfully submitted,

By 

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WHAT IS CLAIMED IS:

1. A method for obtaining a transduced population of viable cells by a retrovirus, comprising:

infecting the cells with a retrovirus in the presence of an effective immobilized amount of material to increase the efficiency of transduction of the cells by the retrovirus, said material including a ligand which binds to the cells and a ligand which binds to the retrovirus, so as to co-localize the retrovirus and the cells, said infecting being conducted in a medium essentially free from a polycationic agent which increases the efficiency of transduction of the cells by the retrovirus in co-culture, but which agent reduces the efficiency of transduction of the cells by the retrovirus in the presence of said material.

2. The method of claim 1 wherein the cells comprise hematopoietic stem cells.

3. A viable cellular population produced by the method of claim 1, which population is essentially free from said polycationic agent and contains said material.

4. The viable cellular population of claim 3 which comprises hematopoietic stem cells.

5. A method for cellular grafting, comprising:

grafting a mammal with a viable mammalian cellular population produced by the method of claim 1, which population is essentially free from said polycationic agent and contains said material.

6. A cellular composition, comprising:

a substantially retroviral-transduced *in vitro* population of viable cells, said composition being essentially free from both retroviral producer cells and a polycationic agent which increases the efficiency of transduction of the cells by the retrovirus in co-culture, said composition further comprising a material including a ligand which binds to the cells and a ligand which binds to the retrovirus.

7. The cellular composition of claim 6 wherein said viable cells comprise hematopoietic stem cells.

8. A method for cellular grafting, comprising:
grafting a mammal with a cellular population according to claim 6.

9. The method of claim 8 wherein the cellular population comprises hematopoietic stem cells.

10. A method for obtaining a transduced population of viable cells by a retrovirus, comprising:

infecting the cells with a retrovirus in the presence of an effective immobilized amount of material to increase the efficiency of transduction of the cells by the retrovirus, said material including a ligand which binds to the cells and a ligand which binds to the retrovirus, so as to co-localize the retrovirus and the cells, said infecting being conducted in a medium essentially free from a polycationic agent which increases the efficiency of transduction of the cells by the retrovirus in co-culture, but which polycationic agent reduces the efficiency of transduction of the cells by the retrovirus in the presence of said material; said infecting forming a population of viable cells transduced at an efficiency greater than that which would be achieved in the presence of said polycationic agent.

13. A method for transducing T cells with a retrovirus, comprising infecting the cells with the retrovirus in the presence of a material including a ligand which binds to the T cells and a ligand which binds to the retrovirus, so as to co-localize the retrovirus and the cells and increase the transduction efficiency of the cells.

14. The method of claim 13 wherein the material is a polypeptide including a first amino acid sequence which binds the T cells and a second amino acid sequence which binds the retrovirus, the second amino acid sequence having the sequence:

Ala Ile Pro Ala Pro Thr Asp Leu Lys Phe Thr Gln Val Thr Pro Thr Ser Leu Ser Ala Gln Trp Thr Pro Pro Asn Val Gln Leu Thr Gly Tyr Arg Val Arg Val Thr Pro Lys Glu Lys Thr Gly Pro Met Lys Glu Ile Asn Leu Ala Pro Asp Ser Ser Ser Val Val Val Ser Gly Leu Met Val Ala Thr Lys Tyr Glu Val Ser Val Tyr Ala Leu Lys Asp Thr Leu Thr Ser Arg Pro Ala Gln Gly Val Val Thr Thr Leu Glu Asn Val Ser Pro Pro Arg Arg Ala Arg Val Thr Asp Ala Thr Glu Thr Thr Ile Thr Ile Ser Trp Arg Thr Lys Thr Glu Thr Ile Thr Gly Phe Gln Val Asp Ala Val Pro Ala Asn Gly Gln Thr Pro Ile Gln Arg Thr Ile Lys Pro Asp Val Arg Ser Tyr Thr Ile Thr Gly Leu Gln Pro Gly Thr Asp Tyr Lys Ile Tyr Leu Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser Pro Val Val Ile Asp Ala Ser Thr Ala Ile Asp Ala Pro Ser Asn Leu Arg Phe Leu Ala Thr Thr Pro Asn Ser Leu Leu Val Ser Trp Gln Pro Pro Arg Ala Arg Ile Thr Gly Tyr Ile Ile Lys Tyr Glu Lys Pro Gly Ser Pro Pro Arg Glu Val Val Pro Arg Pro Arg Pro Gly Val Thr Glu Ala Thr Ile Thr Gly Leu Glu Pro Gly Thr Glu Tyr Thr Ile Tyr Val Ile Ala Leu Lys Asn Asn Gln Lys Ser Glu Pro Leu Ile Gly Arg Lys Lys Thr;

or a sufficiently similar amino acid sequence thereto to exhibit the ability to bind the retrovirus;

16. The method of claim 1, wherein said cells are mammalian cells.

17. The method of claim 16, wherein said cells are human cells.

18. The method of claim 2, wherein said cellular population is a human cellular population comprising hematopoietic stem cells.

19. The viable cellular population of claim 4, wherein said cells are mammalian cells.

20. The viable cellular population of claim 19, wherein the cellular population is a human hematopoietic cellular population containing hematopoietic stem cells.

21. The method of claim 8, wherein the cellular population is from the same species as the mammal.

22. The method of claim 21, wherein the mammal is a human and the cellular population is a human cellular population.

23. The method of claim 10, wherein the ligand which binds the retrovirus is a polypeptide having a sequence of:

Ala Ile Pro Ala Pro Thr Asp Leu Lys Phe Thr Gln Val Thr Pro Thr Ser Leu Ser Ala Gln Trp Thr Pro Pro Asn Val Gln Leu Thr Gly Tyr Arg Val Arg Val Thr Pro Lys Glu Lys Thr Gly Pro Met Lys Glu Ile Asn Leu Ala Pro Asp Ser Ser Ser Val Val Val Ser Gly Leu Met Val Ala Thr Lys Tyr Glu Val Ser Val Tyr Ala Leu Lys Asp Thr Leu Thr Ser Arg Pro Ala Gln Gly Val Val Thr Thr Leu Glu Asn Val Ser Pro Pro Arg Arg Ala Arg Val Thr Asp Ala Thr Glu Thr Thr Ile Thr Ile Ser Trp Arg Thr Lys Thr Glu Thr Ile Thr Gly Phe Gln Val Asp Ala Val Pro Ala Asn Gly Gln Thr Pro Ile Gln Arg Thr Ile Lys Pro Asp Val Arg Ser Tyr Thr Ile Thr Gly Leu Gln Pro Gly Thr Asp Tyr Lys Ile Tyr Leu Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser Pro Val Val Ile Asp Ala Ser Thr Ala Ile Asp Ala Pro Ser Asn Leu Arg Phe Leu Ala Thr Thr Pro Asn Ser Leu Leu Val Ser Trp Gln Pro Pro Arg Ala Arg Ile Thr Gly Tyr Ile Ile Lys Tyr Glu Lys Pro Gly Ser Pro Pro Arg Glu Val Val Pro Arg Pro Arg Pro Gly Val Thr Glu Ala Thr Ile Thr Gly Leu Glu Pro Gly Thr Glu Tyr Thr Ile Tyr Val Ile Ala Leu Lys Asn Asn Gln Lys Ser Glu Pro Leu Ile Gly Arg Lys Lys Thr;

or a sufficiently similar amino acid sequence thereto to exhibit the ability to bind the retrovirus.

24. The method of claim 23 wherein the cells are human hematopoietic cells, and the material is a polypeptide including an amino acid sequence of:

Ala Ile Pro Ala Pro Thr Asp Leu Lys Phe Thr Gln Val Thr Pro Thr Ser Leu Ser Ala Gln Trp Thr Pro Pro Asn Val Gln Leu Thr Gly Tyr Arg Val Arg Val Thr Pro Lys Glu Lys Thr Gly Pro Met Lys Glu Ile Asn Leu Ala Pro Asp Ser Ser Ser Val Val Val Ser Gly Leu Met Val Ala Thr Lys Tyr Glu Val Ser Val Tyr Ala Leu Lys Asp Thr Leu Thr Ser Arg Pro Ala Gln Gly Val Val Thr Thr Leu Glu Asn Val Ser Pro Pro Arg Arg Ala Arg Val Thr Asp Ala Thr

Glu Thr Thr Ile Thr Ile Ser Trp Arg Thr Lys Thr Glu Thr Ile Thr Gly Phe Gln Val Asp Ala Val Pro Ala Asn Gly Gln Thr Pro Ile Gln Arg Thr Ile Lys Pro Asp Val Arg Ser Tyr Thr Ile Thr Gly Leu Gln Pro Gly Thr Asp Tyr Lys Ile Tyr Leu Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser Pro Val Val Ile Asp Ala Ser Thr Ala Ile Asp Ala Pro Ser Asn Leu Arg Phe Leu Ala Thr Thr Pro Asn Ser Leu Leu Val Ser Trp Gln Pro Pro Arg Ala Arg Ile Thr Gly Tyr Ile Ile Lys Tyr Glu Lys Pro Gly Ser Pro Pro Arg Glu Val Val Pro Arg Pro Arg Pro Gly Val Thr Glu Ala Thr Ile Thr Gly Leu Glu Pro Gly Thr Glu Tyr Thr Ile Tyr Val Ile Ala Leu Lys Asn Asn Gln Lys Ser Glu Pro Leu Ile Gly Arg Lys Lys Thr;

or a sufficiently similar amino acid sequence thereto to exhibit the ability to bind the retrovirus;

and an amino acid sequence of:

Asp Glu Leu Pro Gln Leu Val Thr Leu Pro His Pro Asn Leu His Gly Pro Glu Ile Leu Asp Val Pro Ser Thr;

or a sufficiently similar amino acid sequence thereto to exhibit the ability to bind hematopoietic cells.

25. The method of claim 10 wherein the cells are mammalian cells, and said infecting is conducted in a medium free from retroviral co-producer cells.

ABSTRACT OF THE DISCLOSURE

A method to increase the efficiency of transduction of hematopoietic and other cells by retroviruses includes infecting the cells in the presence of fibronectin or fibronectin fragments. The fibronectin and fibronectin fragments significantly enhance retroviral-mediated gene transfer into the cells, particularly hematopoietic cells including committed progenitors and primitive hematopoietic stem cells. The invention also provides improved methods for somatic gene therapy capitalizing on enhanced gene transfer, hematopoietic cellular populations, and novel constructs for enhancing retroviral-mediated DNA transfer into cells and their use.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PCT application of INDIANA UNIVERSITY FOUNDATION	Authorized Officer Richard B. Lazarus
International Application Number PCT/US96/15712	Mailing Date 3 February 1997
International Filing Date 30 September 1996	Agent's File Reference: IU33CIP-3PCT
Title of Invention METHODS FOR ENHANCED VIRUS-MEDIATED DNA TRANSFER USING MOLECULES WITH VIRUS-AND CELL-BINDING	

RESPONSE TO THE INVITATION TO CORRECT DEFECTS IN THE INTERNATIONAL APPLICATION

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Attention: RO/US

Dear Sir/Madam:

In response to the Invitation to Correct Defects in the International Application, Applicant previously requested an extension of time in which to submit formal drawings for FIGS. 4 and 11-27. Enclosed herewith are the formal drawings. FIGS. 4 and 11 are believed to be good, clean photocopies of the photographs for printing purposes. However, if these two figures are not suitable, please see the file for PCT/US95/03817, having the same Applicant, INDIANA UNIVERSITY FOUNDATION, as FIGs. 4 and 11 were submitted in photograph form (Figs. 4 and 11) in that case.

Respectfully submitted

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Signature of person mailing paper or fee

By Timothy N. Thomas

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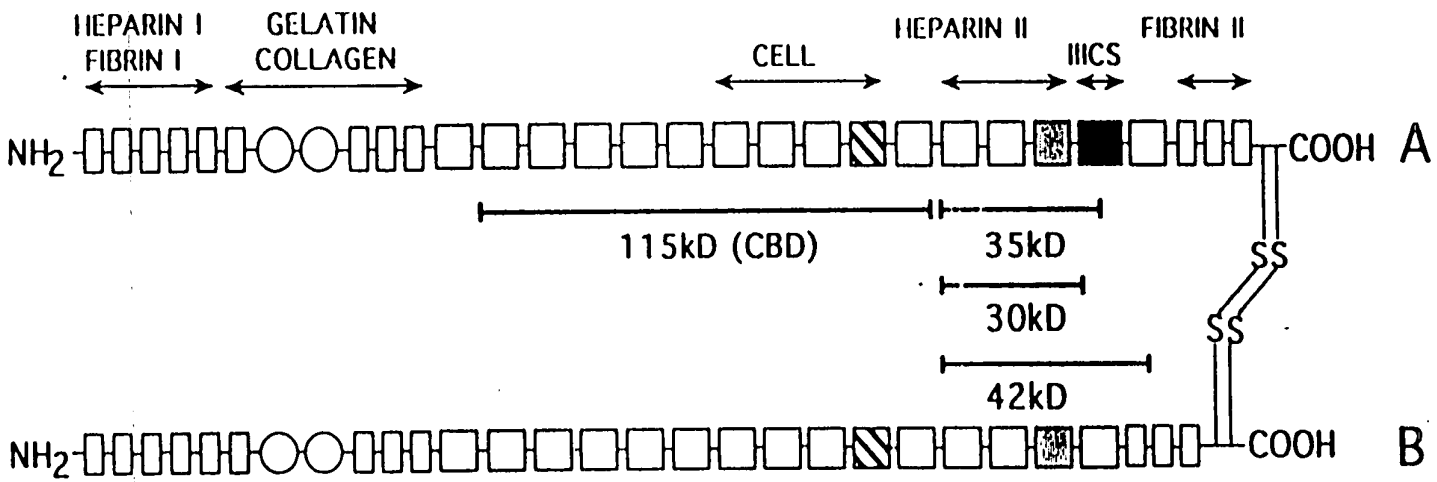
0704i
Enclosures: Figs. 4 and 11-27


HEPARIN I
FIBRIN I
GELATIN
COLLAGEN
CELL
HEPARIN II
IIICS
FIBRIN II
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35kD
30kD
42kD
SS
SS
NH2
COOH
B

FIG. 1

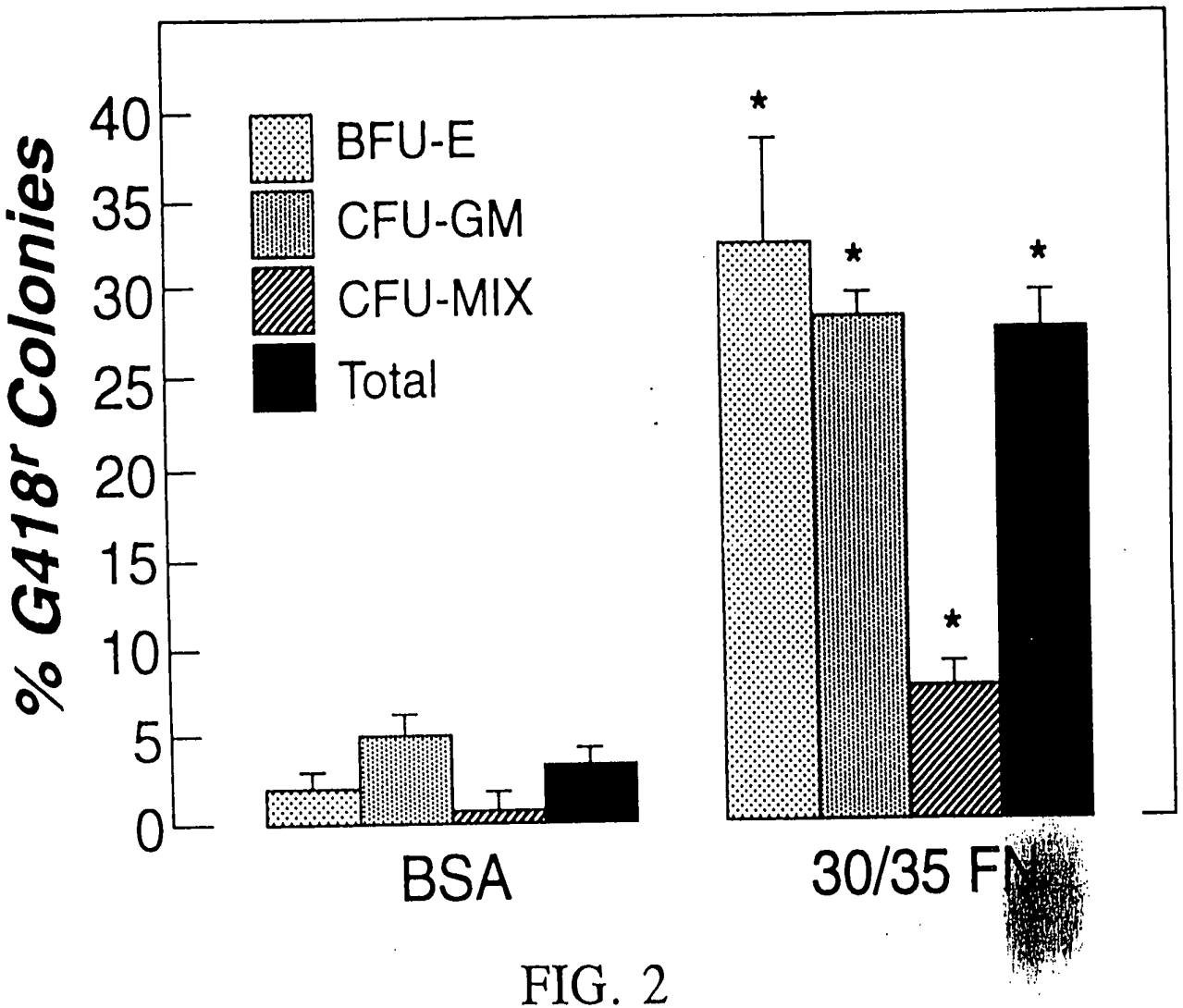

% G418r Colonies
40
35
30
25
20
15
10
5
0
BFU-E
CFU-GM
CFU-MIX
Total
*
*
*
*
BSA
30/35 FN

FIG. 2

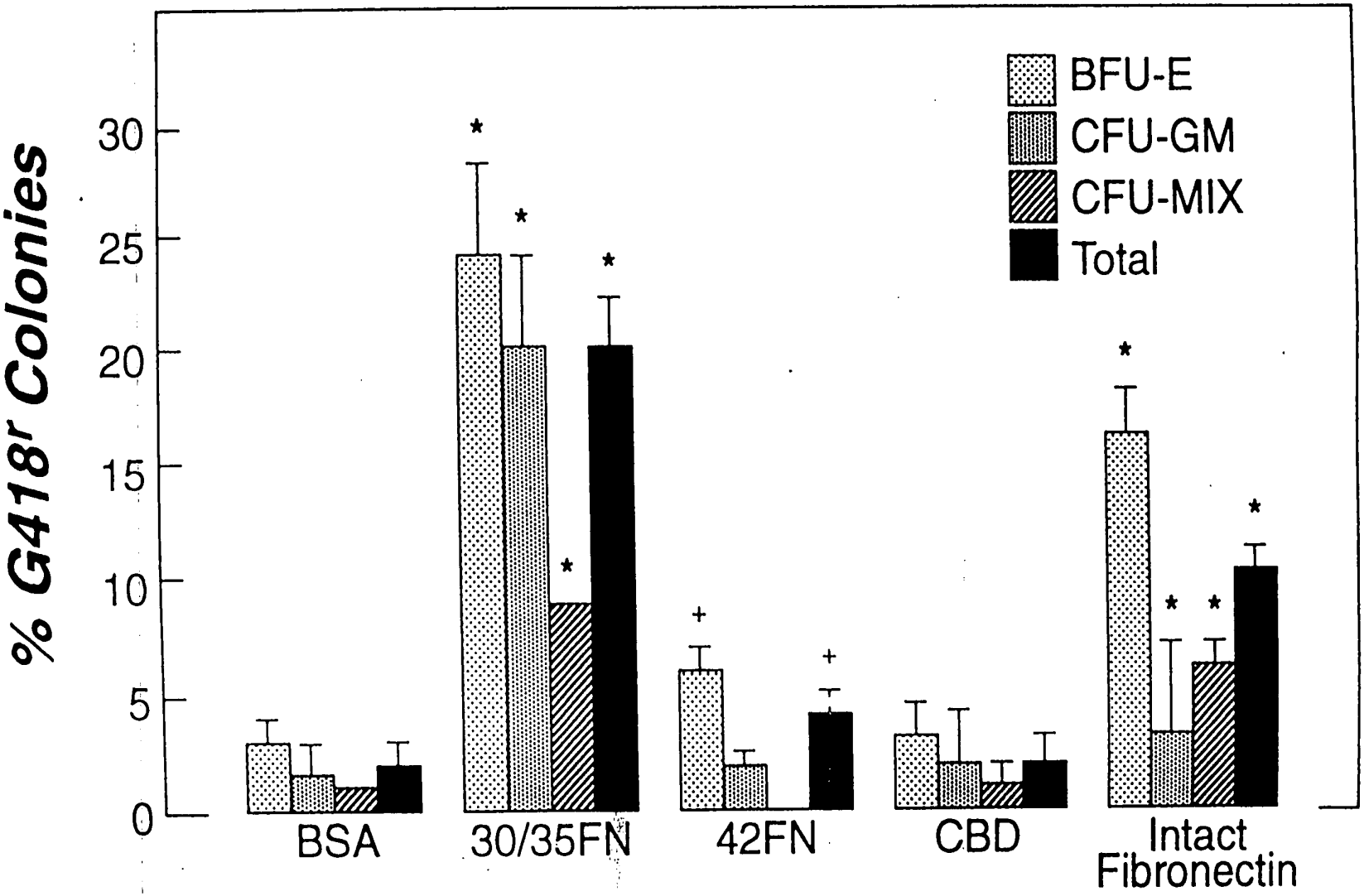

% G418r Colonies
30
25
20
15
10
5
0
BFU-E
CFU-GM
CFU-MIX
Total
BSA
30/35FN
42FN
CBD
Intact Fibronectin

FIG. 3

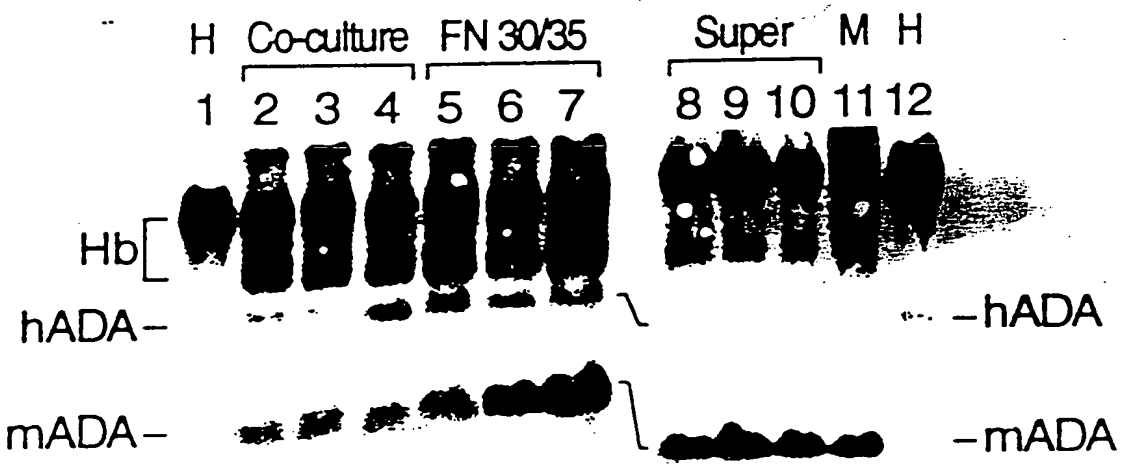

H
Co-culture
FN 30/35
Super
M
H
1 2 3 4 5 6 7
8 9 10 11 12
Hb
hADA–
–hADA
mADA–
–mADA

FIG. 4

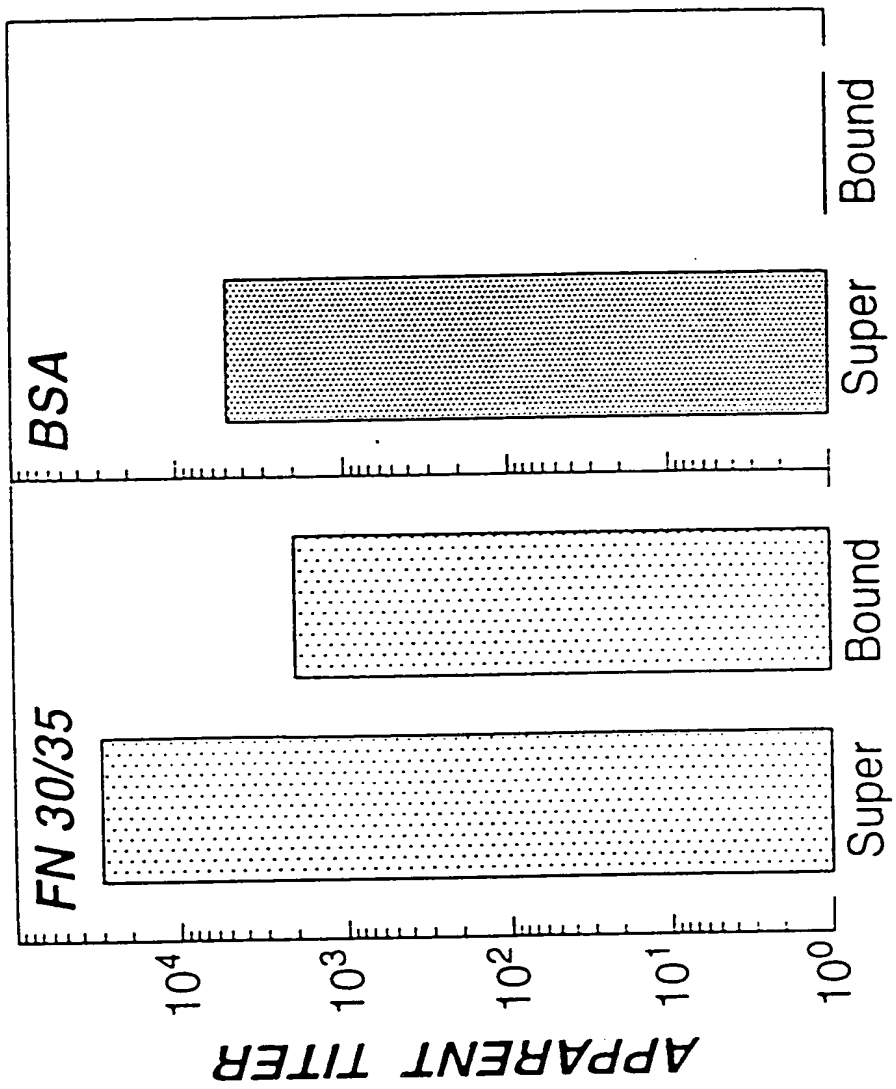

APPARENT TITER
10^4
10^3
10^2
10^1
10^0
FN 30/35
Super
Bound
BSA
Super
Bound

FIG. 5

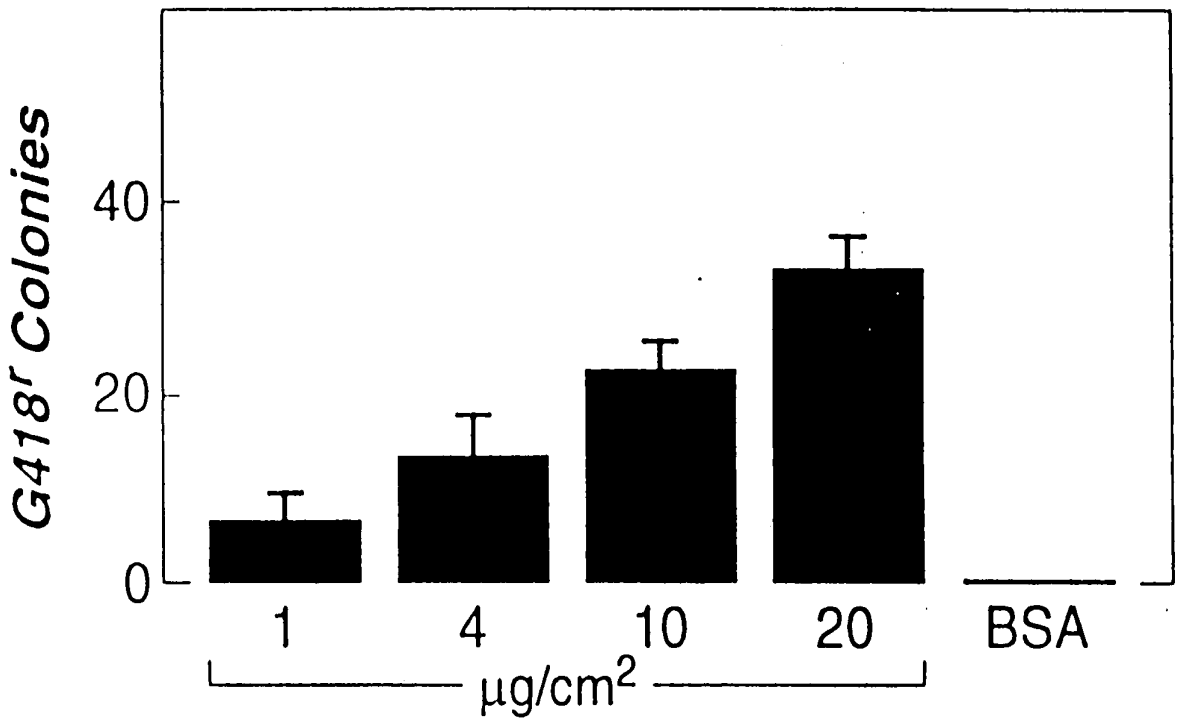


FIG. 6

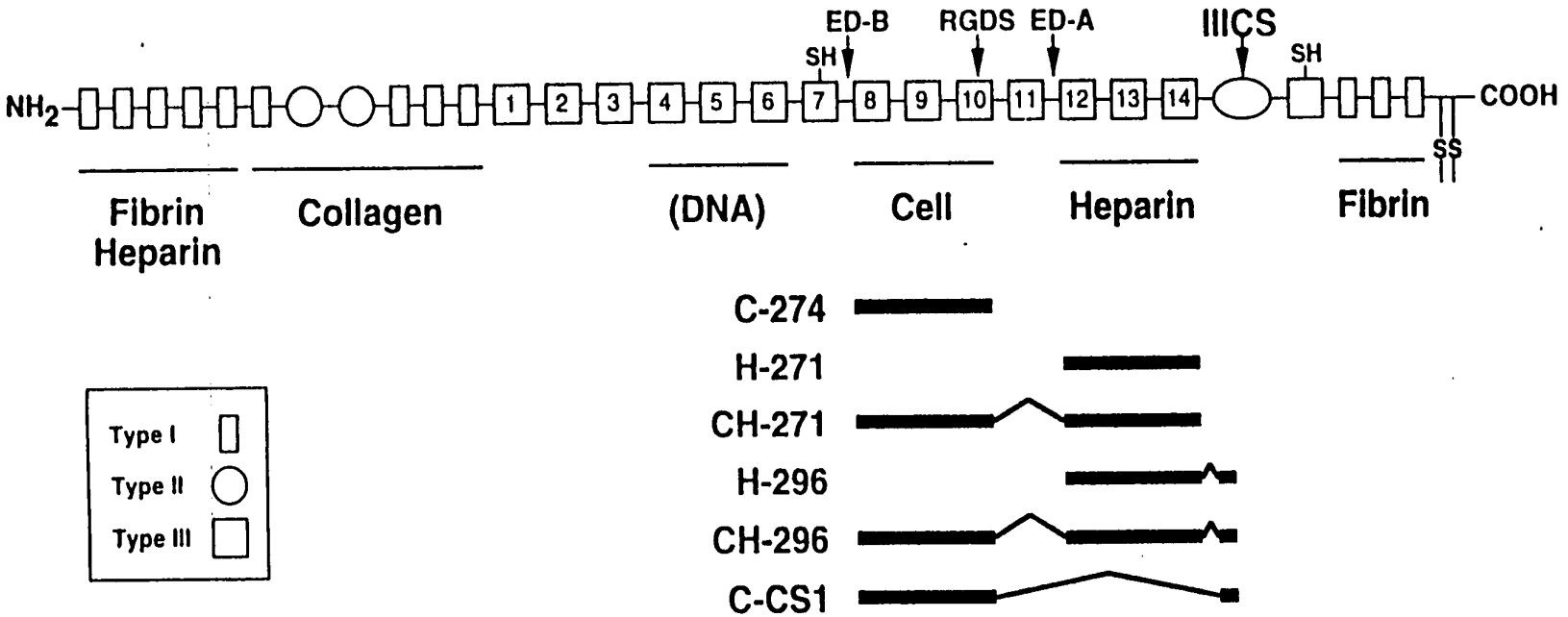

ED-B
RGDS
ED-A
IIICS
SH
SH
NH2
COOH
1
2
3
4
5
6
7
8
9
10
11
12
13
14
SS
Fibrin
Heparin
Collagen
(DNA)
Cell
Heparin
Fibrin
Type I
Type II
Type III
C-274
H-271
CH-271
H-296
CH-296
C-CS1

FIG. 7

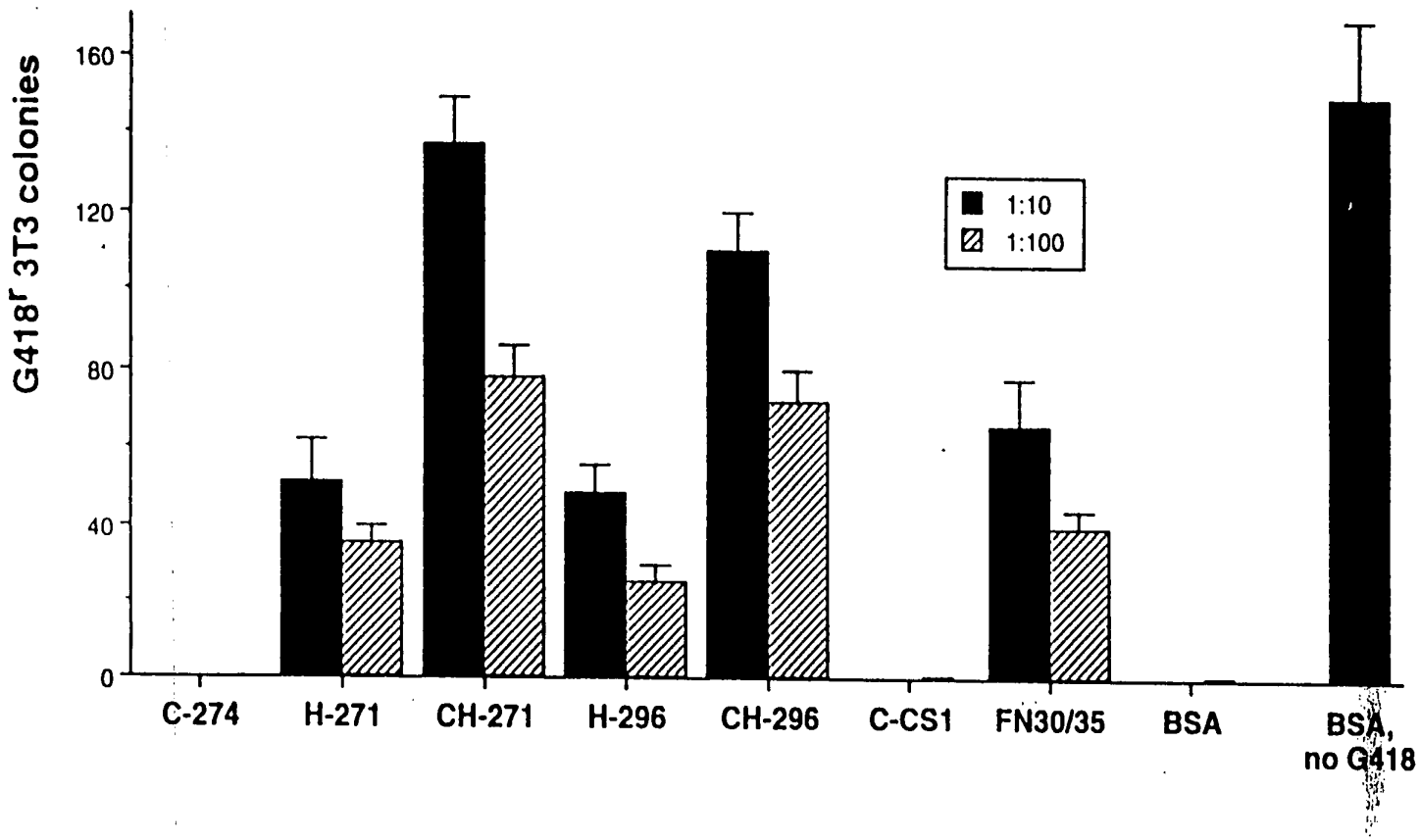

G418r 3T3 colonies
160
120
80
40
0
1:10
1:100
C-274
H-271
CH-271
H-296
CH-296
C-CS1
FN30/35
BSA
BSA, no G418

FIG. 8

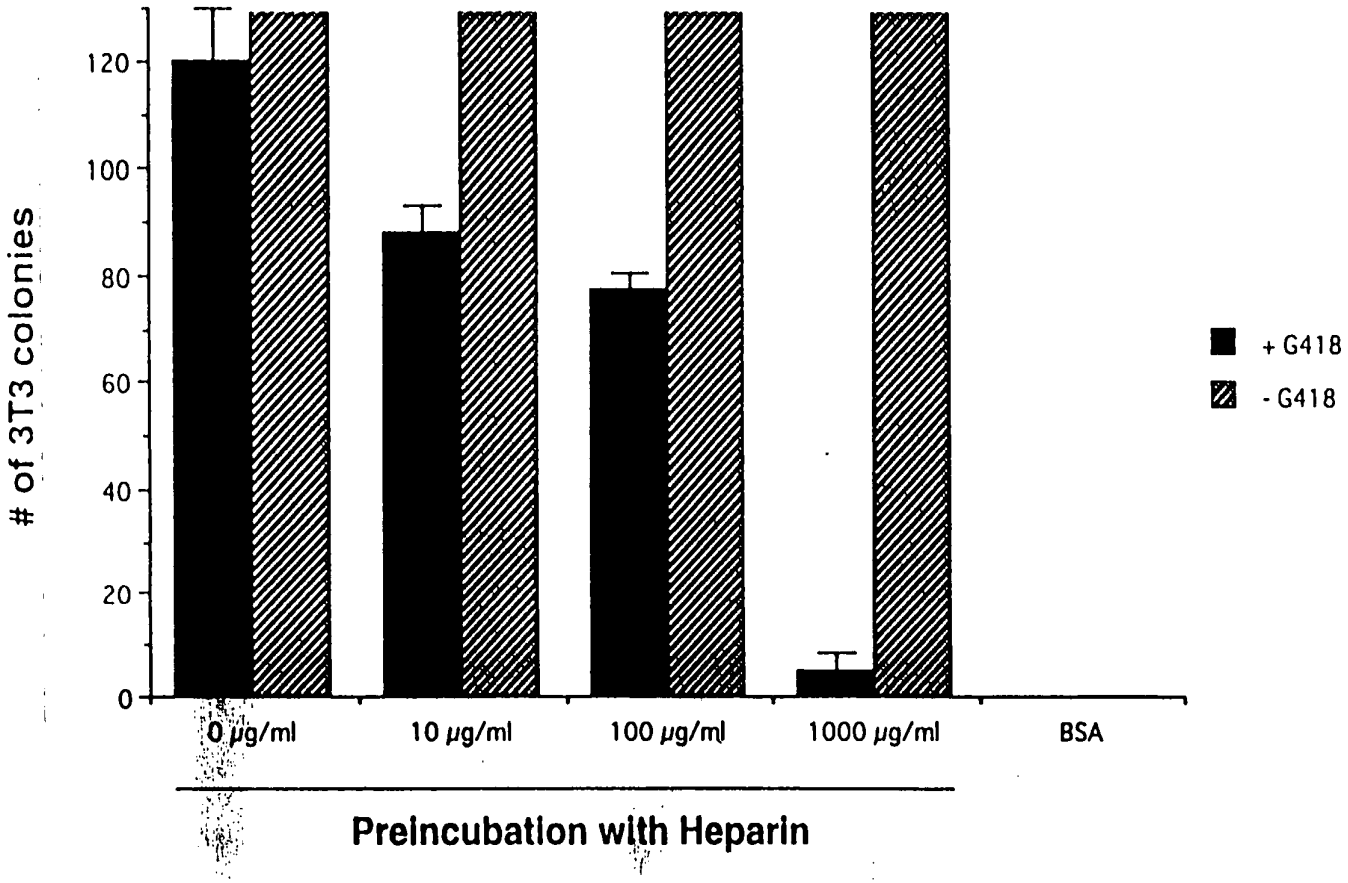

# of 3T3 colonies
120
100
80
60
40
20
0
0 µg/ml
10 µg/ml
100 µg/ml
1000 µg/ml
BSA
Preincubation with Heparin
+ G418
- G418

FIG. 9

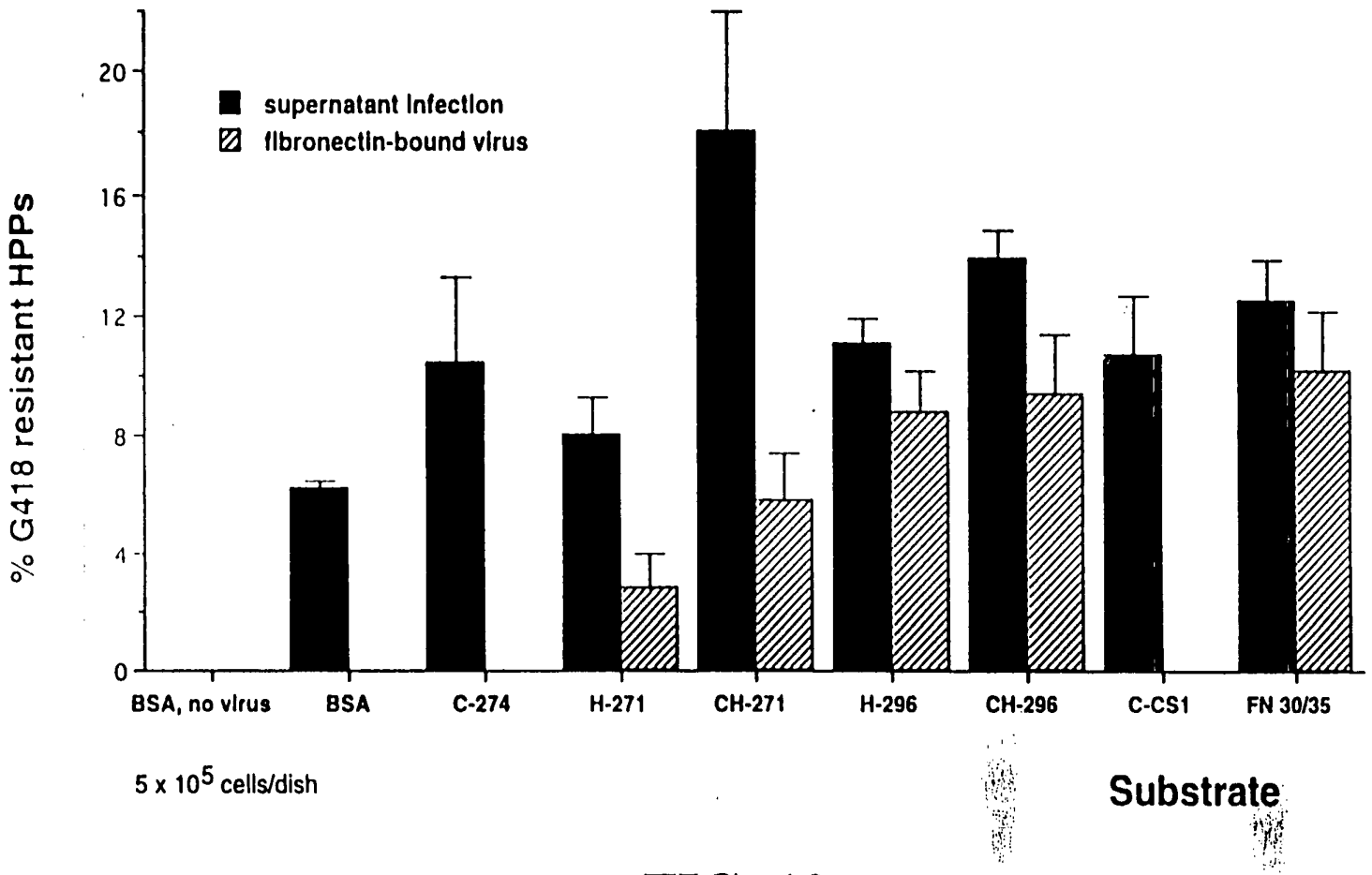

% G418 resistant HPPs
20
16
12
8
4
0
supernatant infection
fibronectin-bound virus
BSA, no virus
BSA
C-274
H-271
CH-271
H-296
CH-296
C-CS1
FN 30/35
5 x 10^5 cells/dish
Substrate

FIG. 10

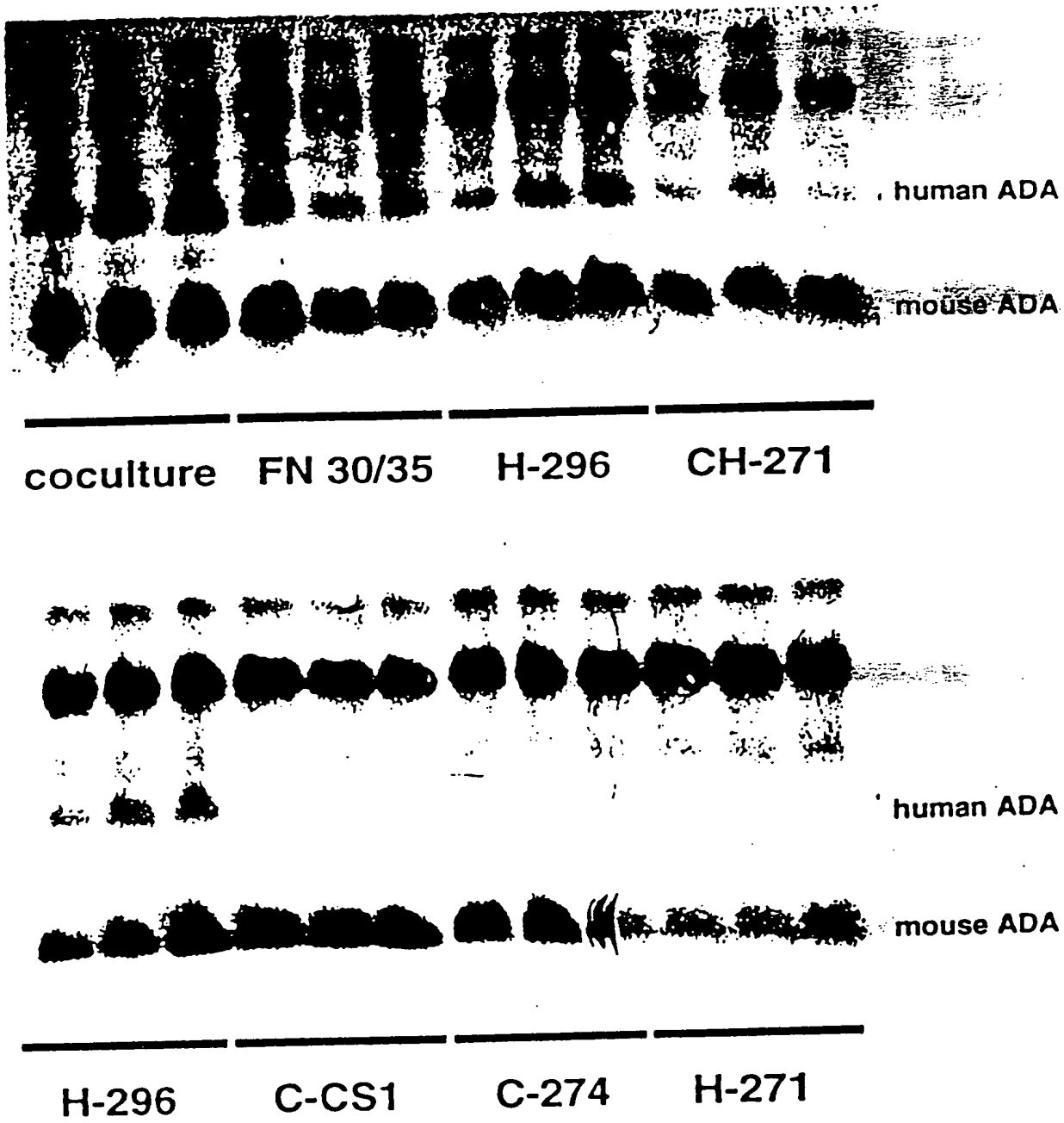
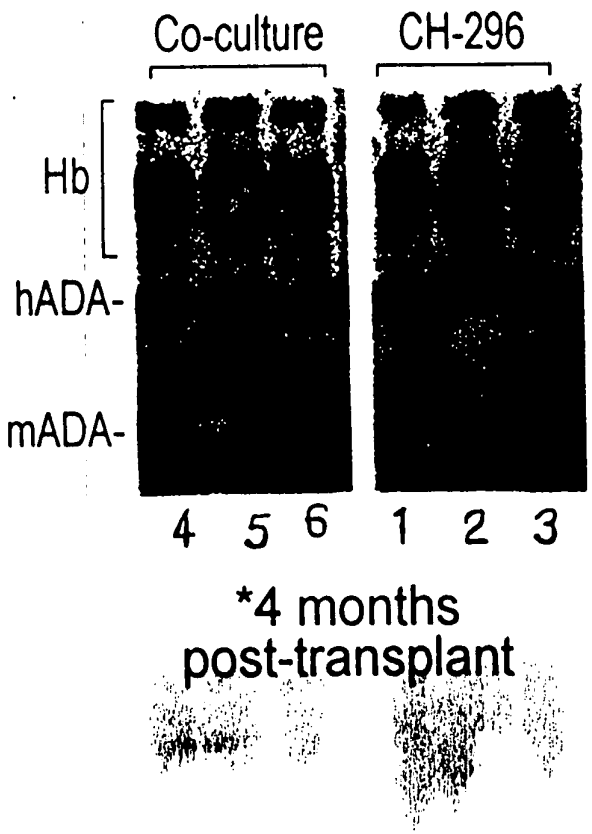

human ADA
mouse ADA
coculture
FN 30/35
H-296
CH-271
human ADA
mouse ADA
H-296
C-CS1
C-274
H-271

FIG. 11

EXPRESSION OF HUMAN ADA AFTER LONG TERM RECONSTITUTION* IN MICE



EXPRESSION OF HUMAN ADA AFTER LONG TERM RECONSTITUTION* IN MICE

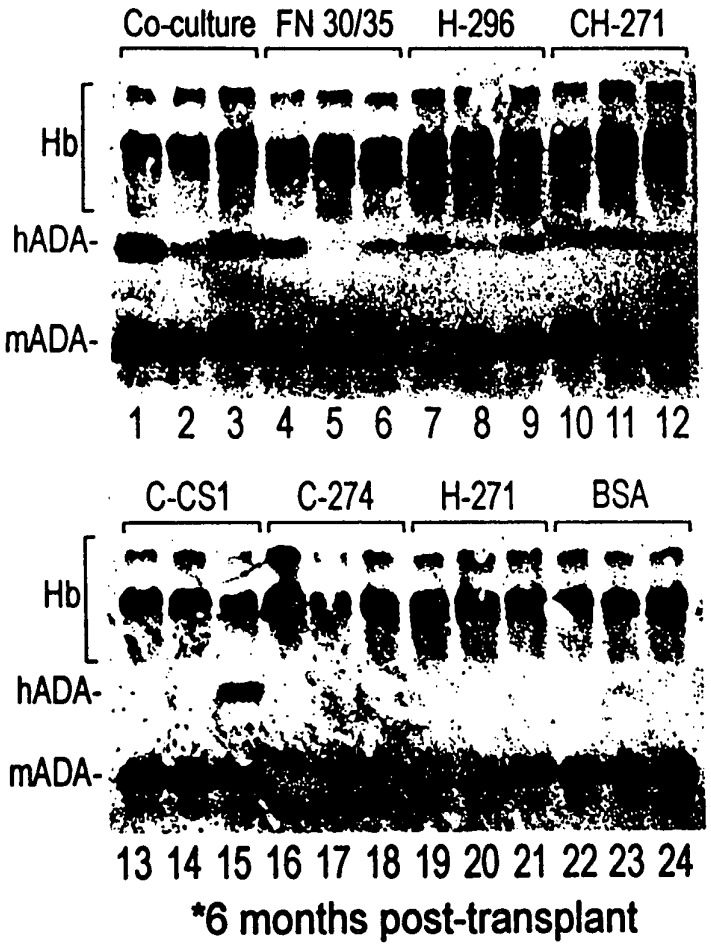
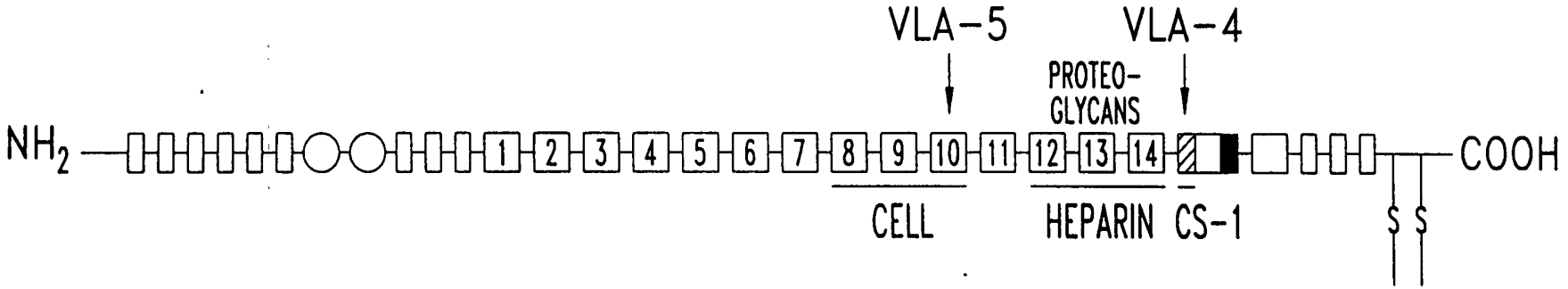
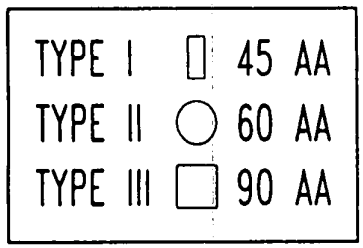


FIG. 12

Recombinant Fibronectin Fragments





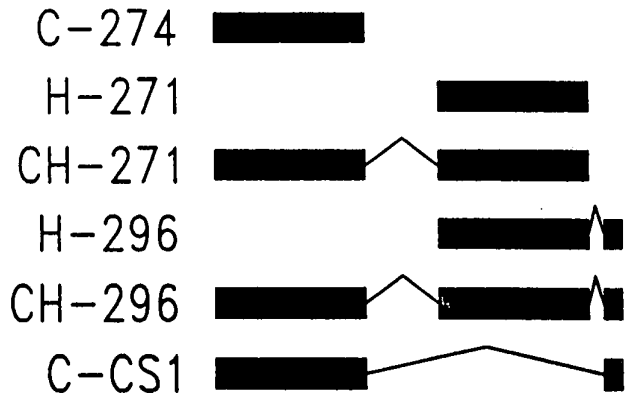


Fig. 13

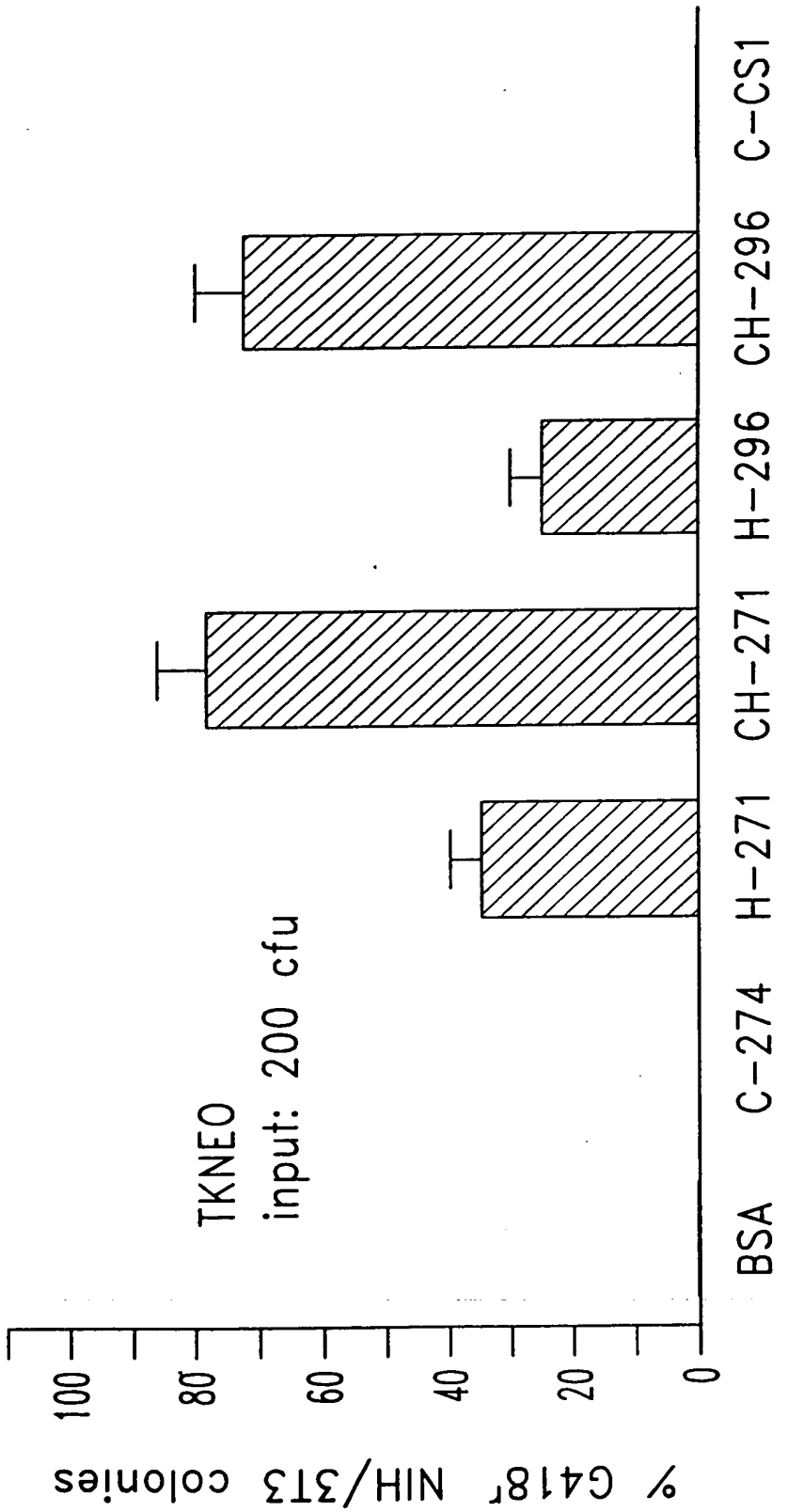

Retrovirus Binds to Fibronectin Fragments
TKNEO
input: 200 cfu
% G418r NIH/3T3 colonies
100
80
60
40
20
0
BSA
C-274
H-271
CH-271
H-296
CH-296
C-CS1
Fibronectin Fragments

Fig. 14

GENE TRANSFER INTO HL60 CELLS

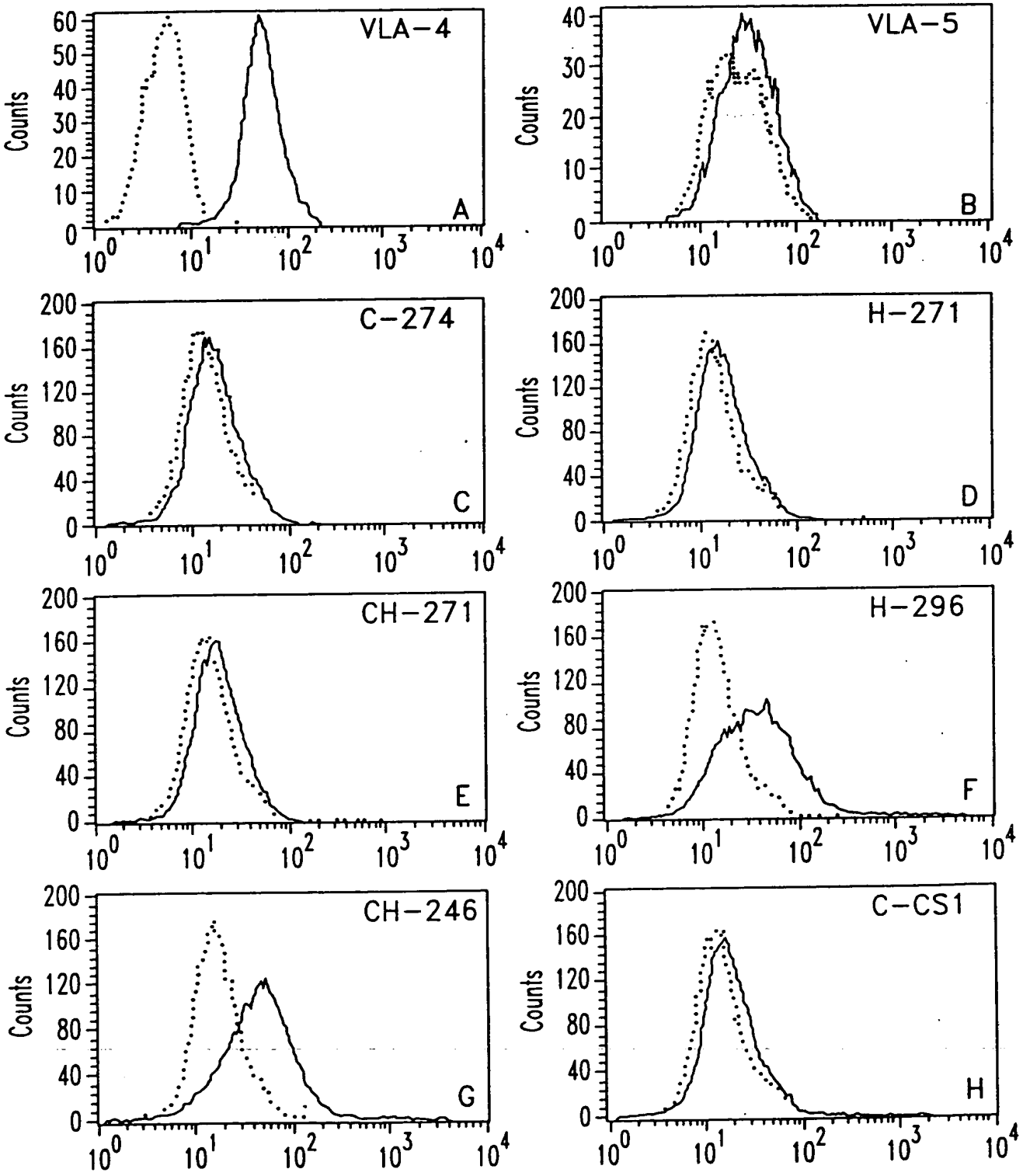


Fig. 15

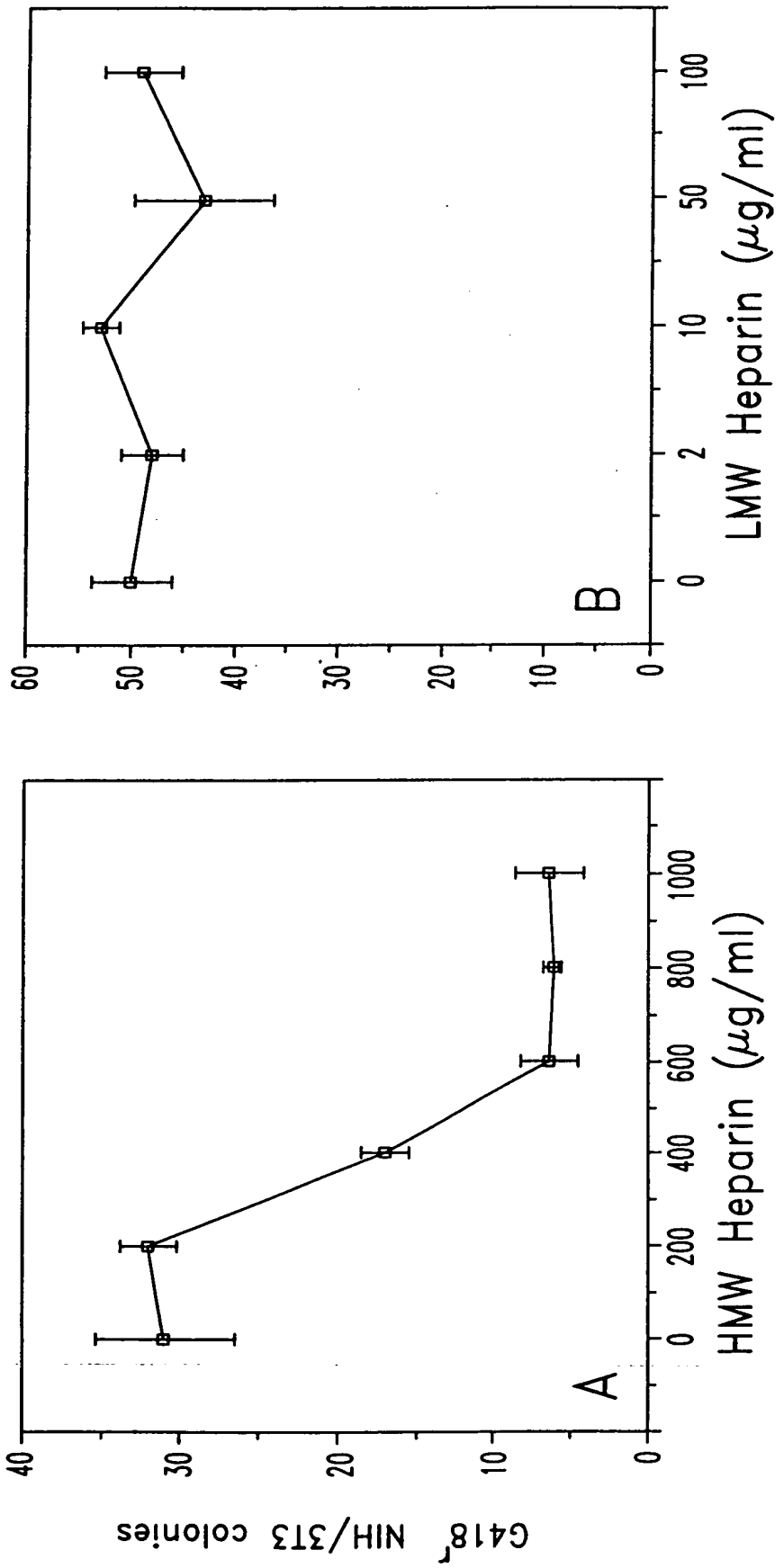

G418r NIH/3T3 colonies
A
HMW Heparin (μg/ml)
0
200
400
600
800
1000
0
10
20
30
40
B
LMW Heparin (μg/ml)
0
2
10
50
100
0
10
20
30
40
50
60

Fig. 16

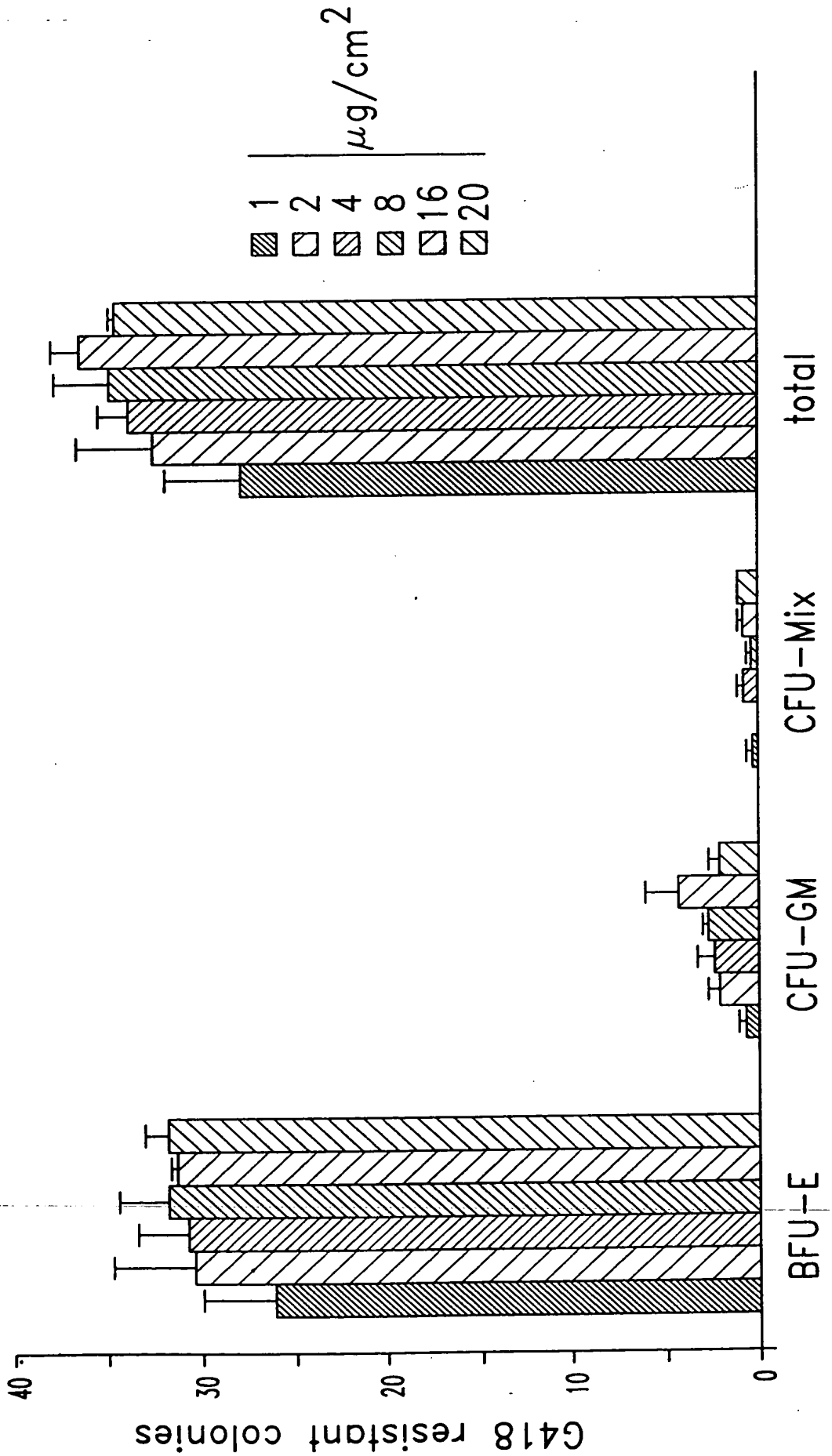

GENE TRANSFER ON CH-271 - CD34+CB CELLS
G418 resistant colonies
40
30
20
10
0
1
2
4
8
16
20
μg/cm2
BFU-E
CFU-GM
CFU-Mix
total

Fig. 17

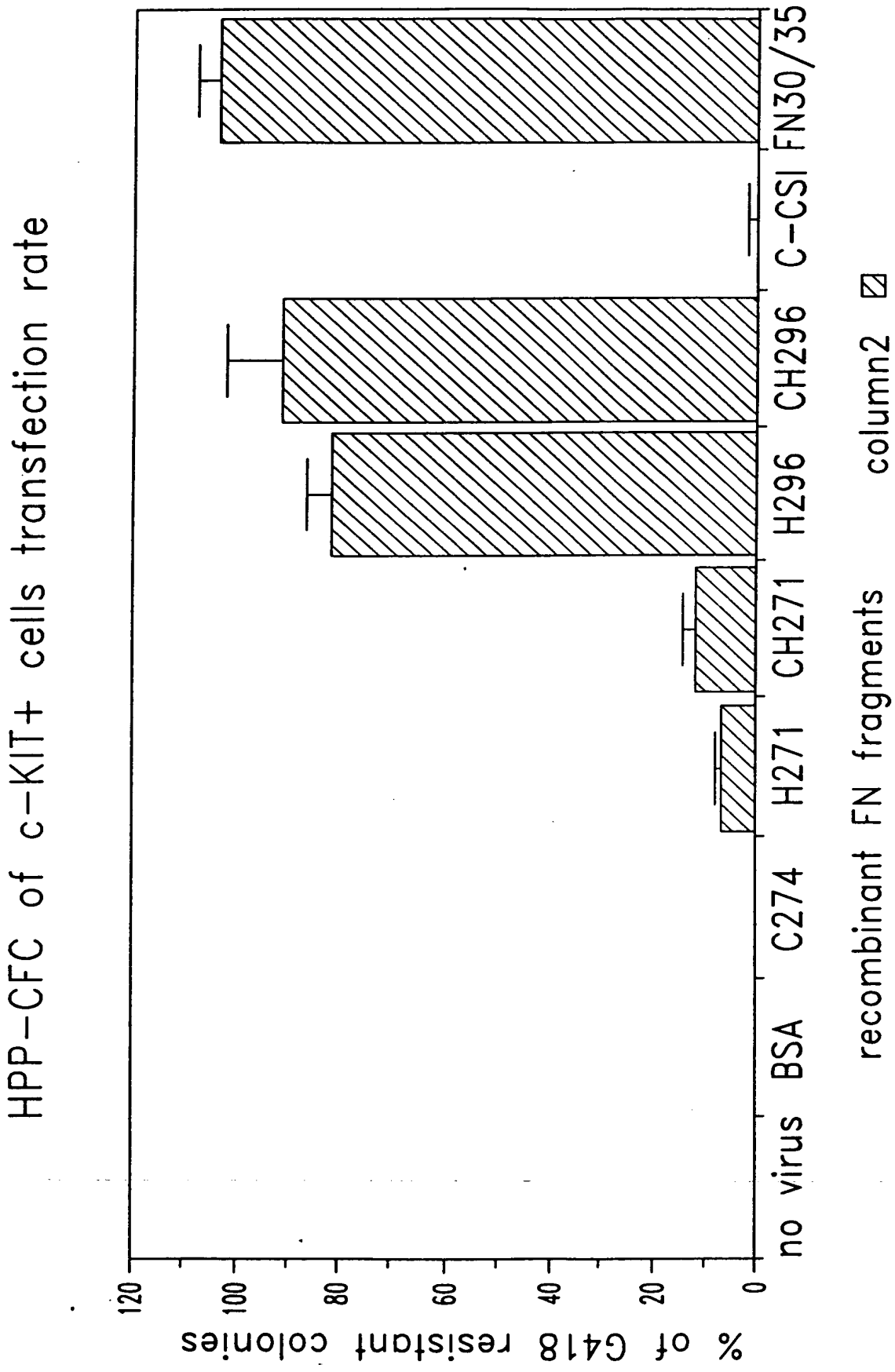

HPP-CFC of c-KIT+ cells transfection rate
% of G418 resistant colonies
120
100
80
60
40
20
0
no virus
BSA
C274
H271
CH271
H296
CH296
C-CSI FN30/35
recombinant FN fragments
column2

Fig. 18

POLYBRENE & GENE TRANSFER INTO FIBROBLASTS

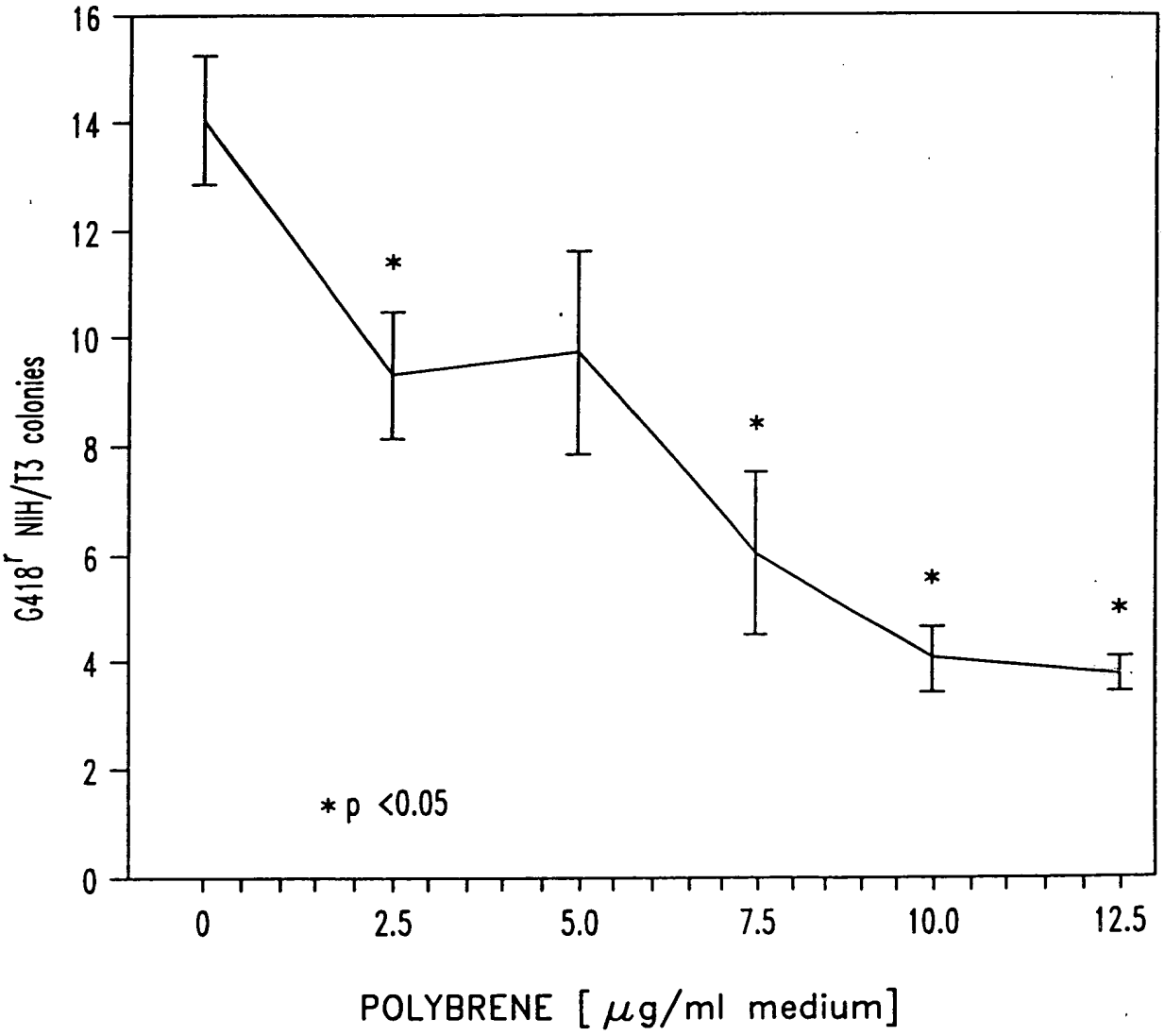


Fig 19

POLYBRENE & GENE TRANSFER INTO CLONOGENIC BM CELLS

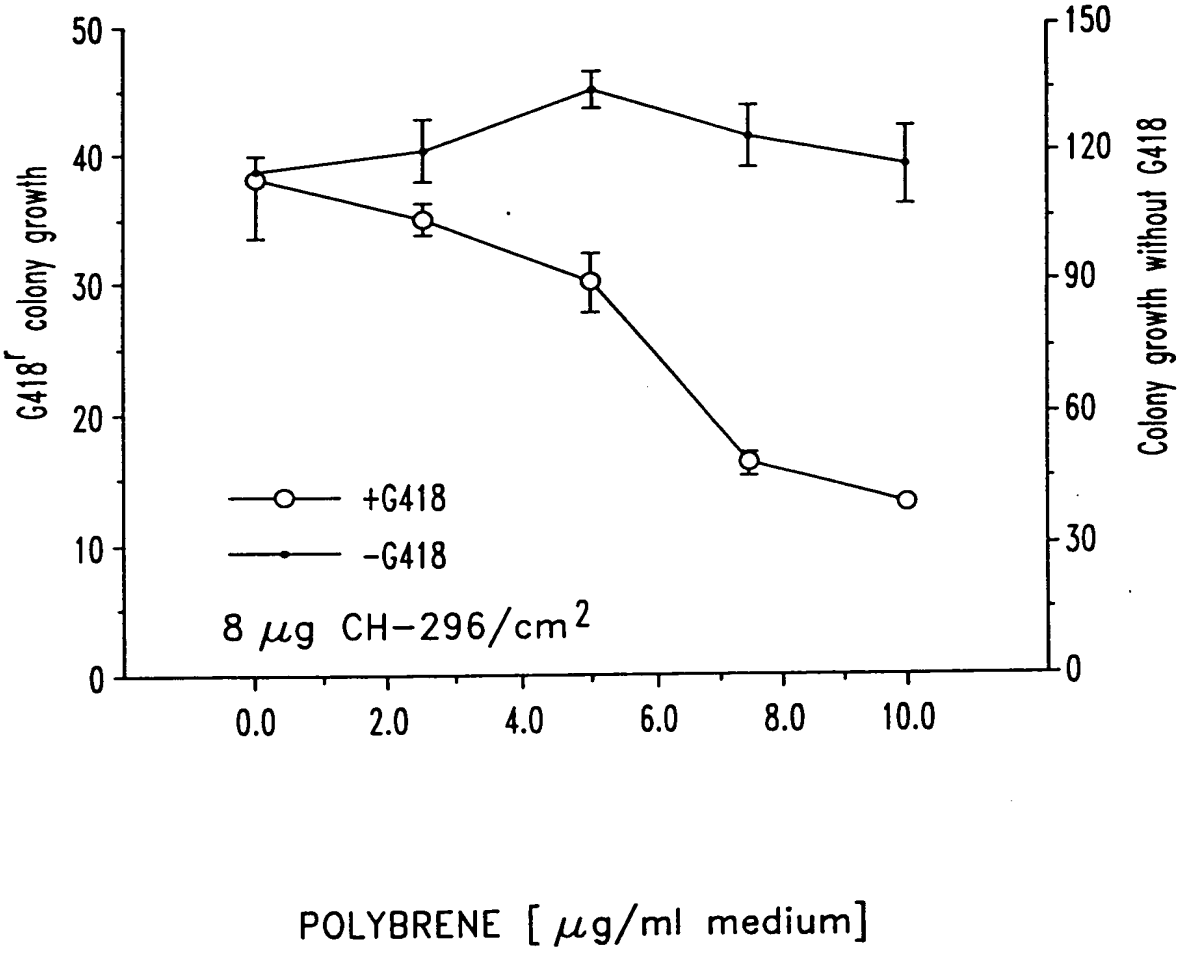


Fig. 20

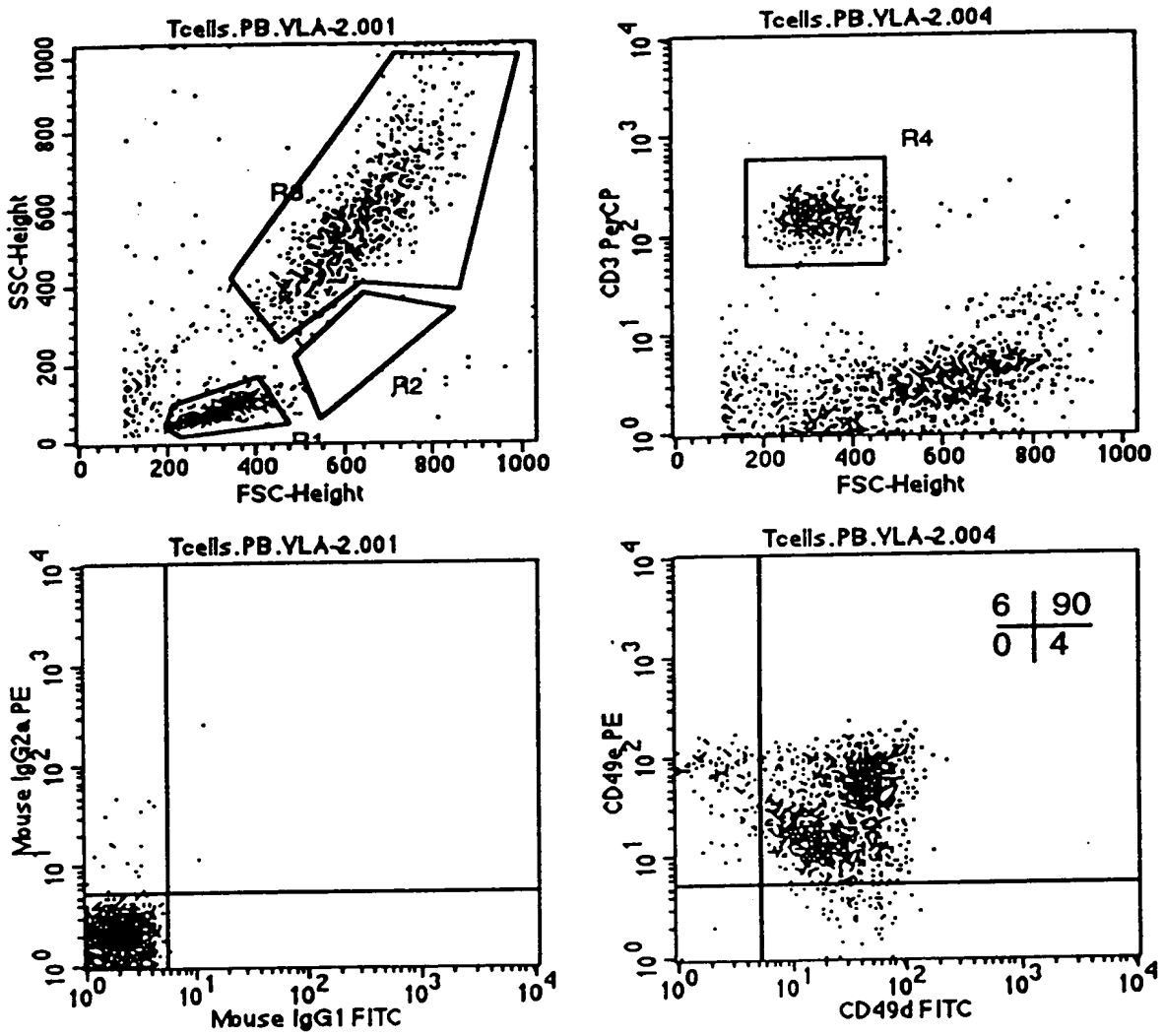

Tcells.PB.VLA-2.001
SSC-Height
FSC-Height
R3
R2
R1
Tcells.PB.VLA-2.004
CD3 PerCP
FSC-Height
R4
Tcells.PB.VLA-2.001
Mouse IgG2a PE
Mouse IgG1 FITC
Tcells.PB.VLA-2.004
CD49e PE
CD49d FITC
6 | 90
0 | 4

FIG. 21

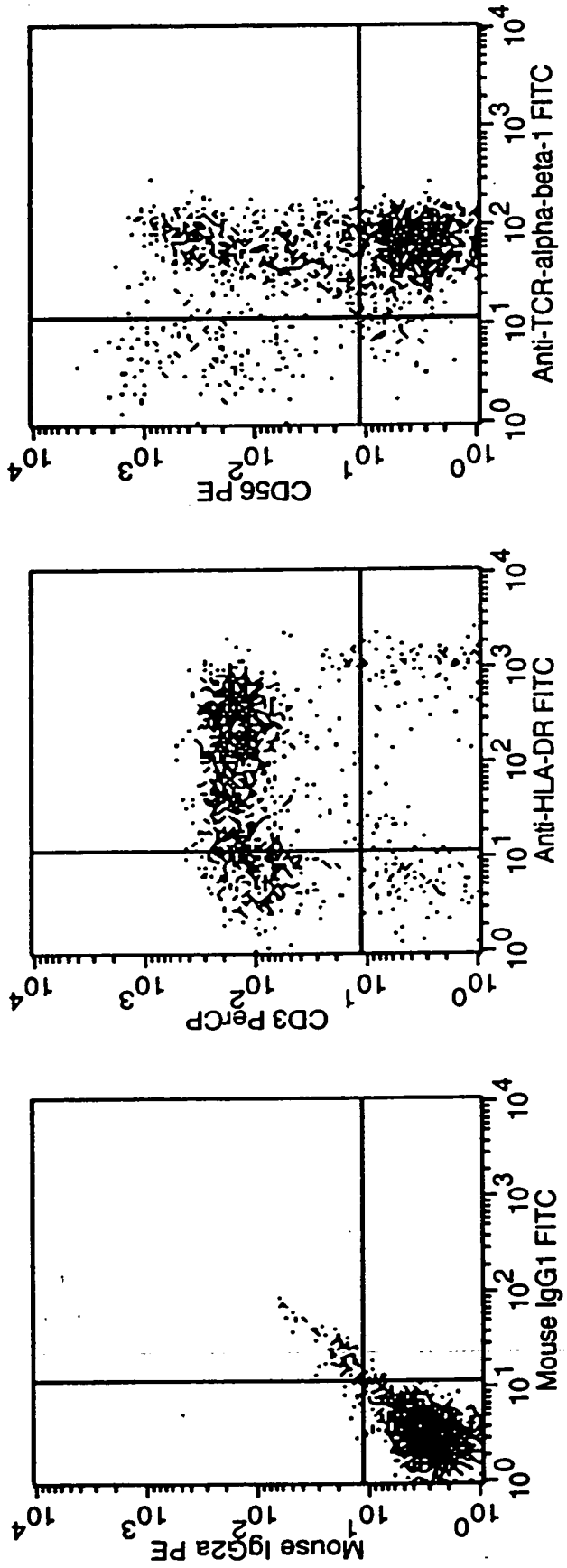


Figure 22: T Cell Activation Status

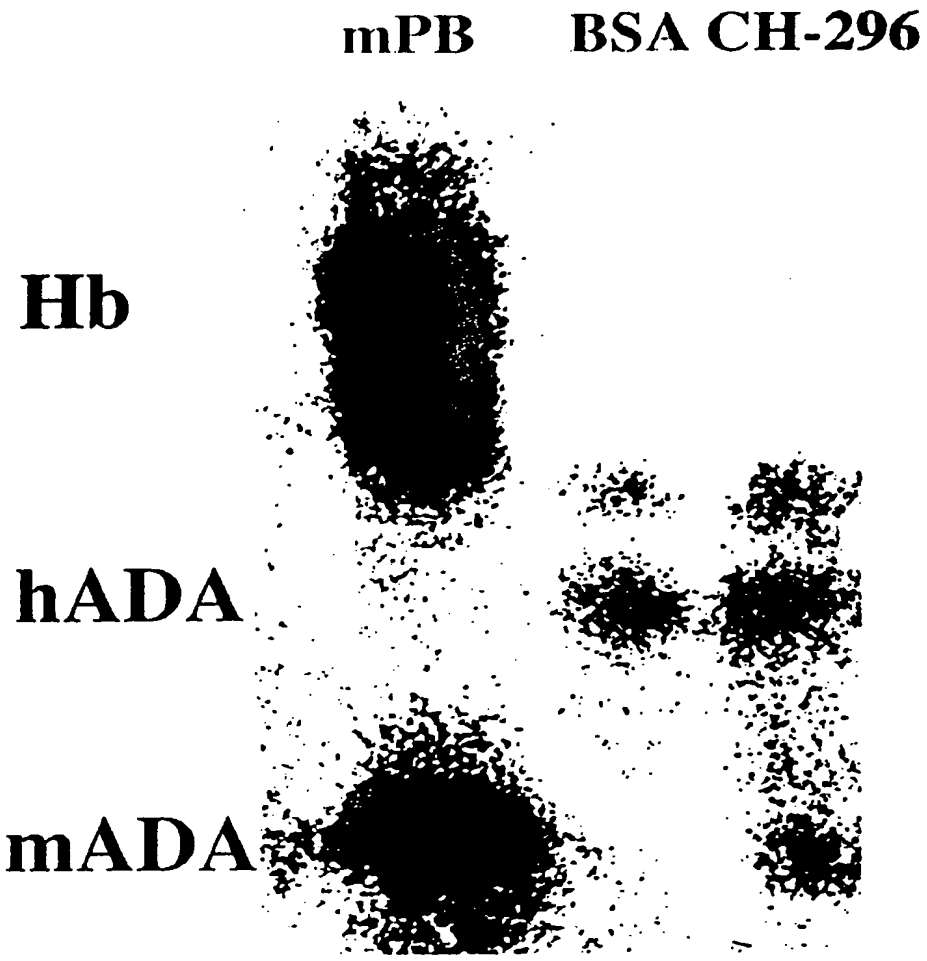
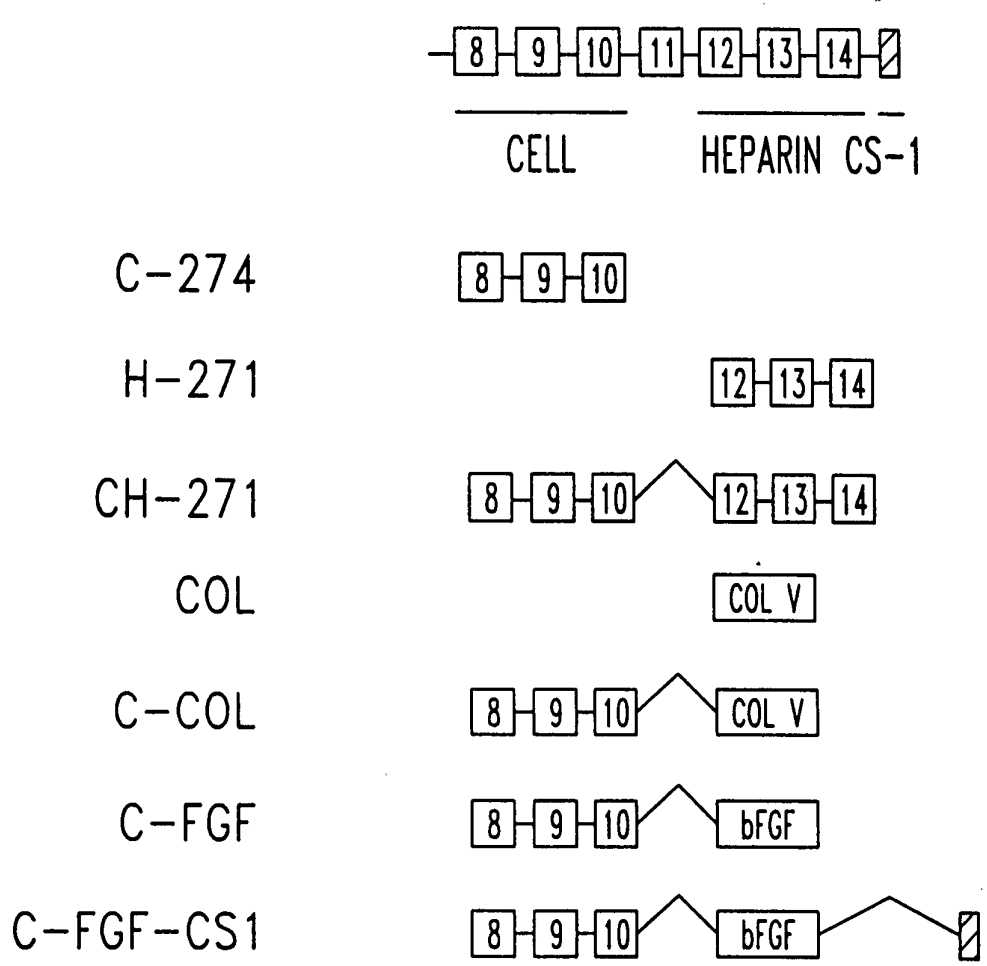
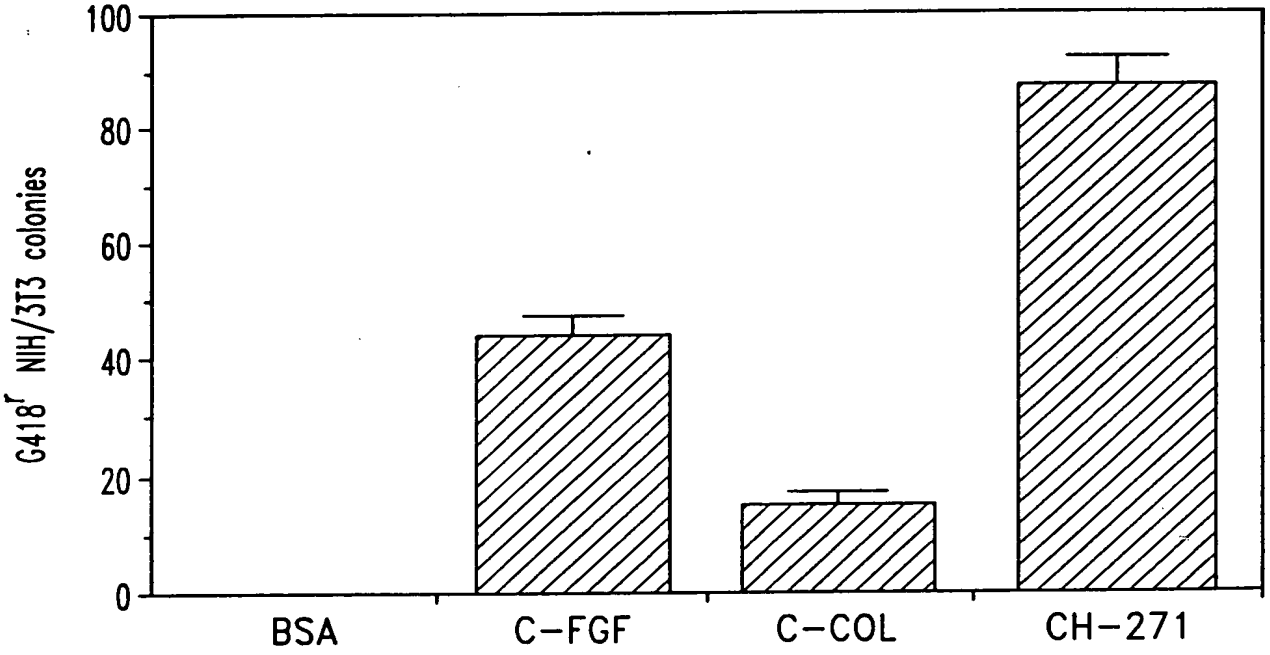


FIG.23



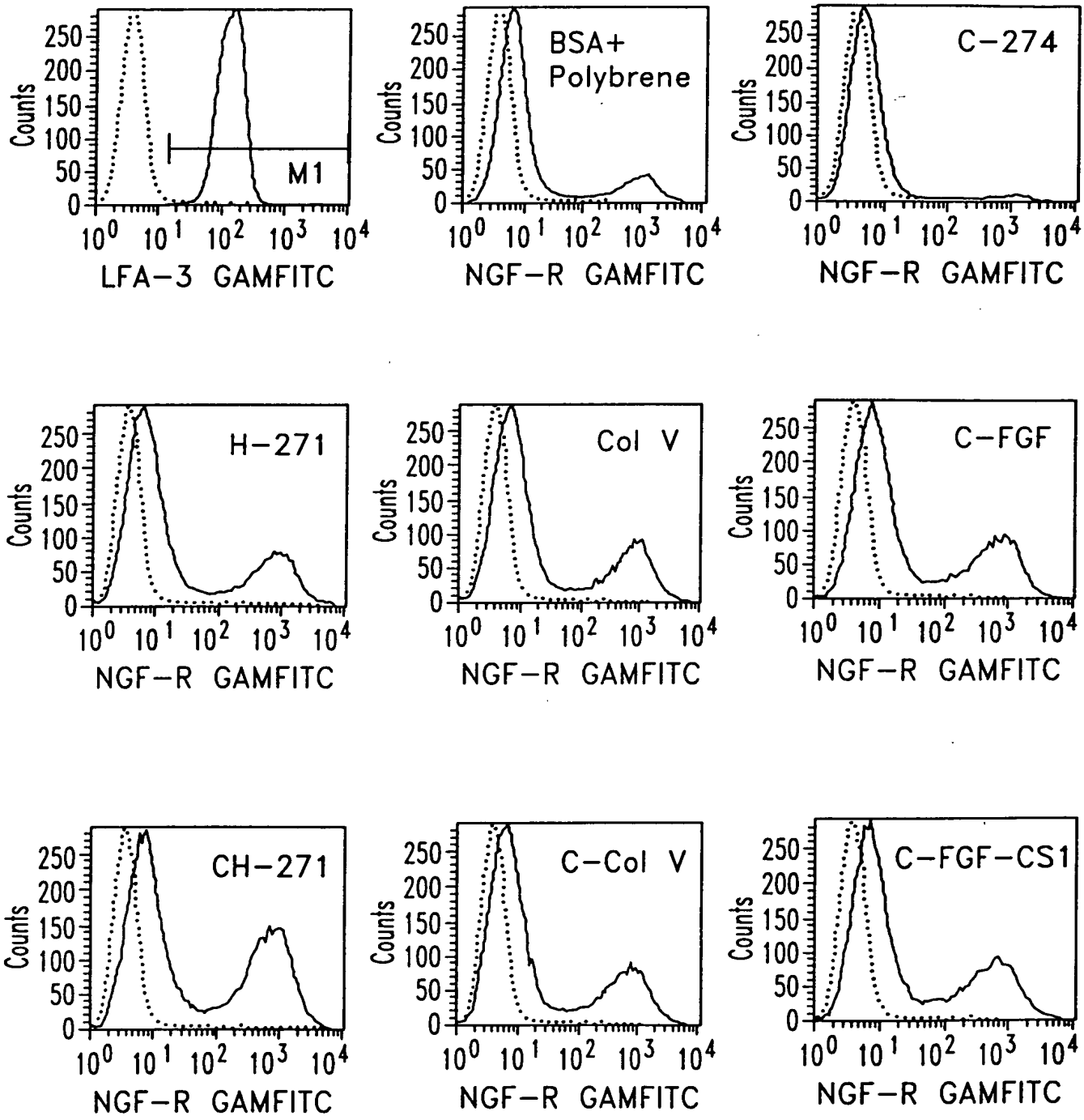
Structure of the recombinant Peptides

Fig. 24



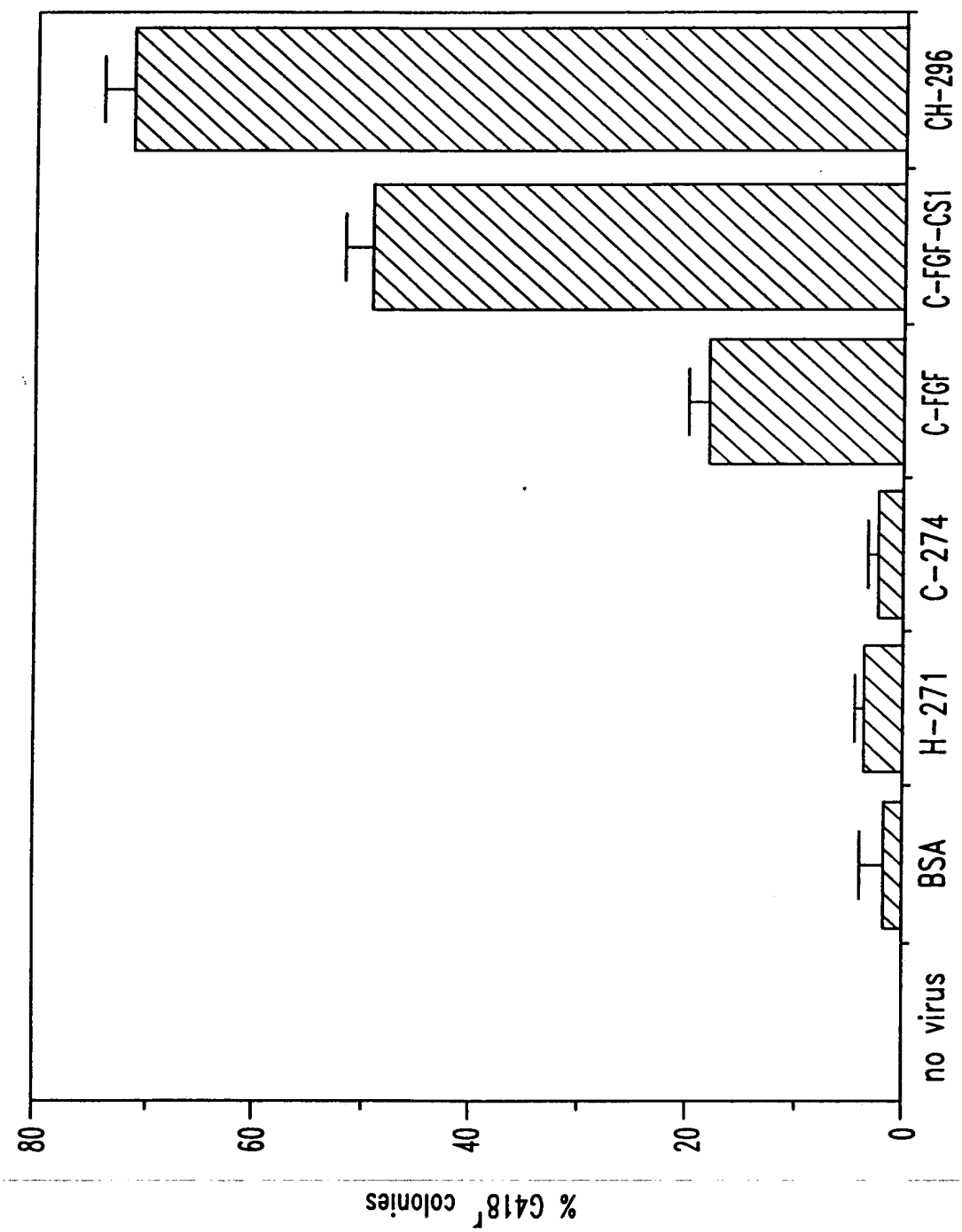
Retrovirus Binding Sequences in COL and bFGF

Fig. 25



Gene Transfer Into HEL Cells

Fig 26



Gene Transfer into CD34+ BM Cells

Fig. 27

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PCT application of INDIANA UNIVERSITY FOUNDATION	)	Authorized Officer Yvette Simms
International Application Number PCT/US96/15712	)	Mailing Date 22 November 1996
International Filing Date 30 September 1996	)	Agent's File Reference: IU33CIP-3PCT
Title of Invention METHODS FOR ENHANCED VIRUS-MEDIATED DNA TRANSFER USING MOLECULES WITH VIRUS-AND CELL-BINDING	)	

RESPONSE TO INVITATION TO CORRECT DEFECTS IN THE INTERNATIONAL APPLICATION

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Attention: RO/US

Dear Sir/Madam:

In response to the Invitation to Correct Defects in the International Application, mailed 22 October 1996, Applicant submits herewith an Appointment of Agent by David A. Williams, a copy of a General Power of Attorney signed by Indiana University Foundation, page one of the request with the correct zip code of Indiana University Foundation as 47402 and not 47404 and formal drawings for FIGS. 1-3 and 5-10. In addition, applicant requests an extension of time in which to file formal drawings for FIGS. 4 and 11-27.

"Express Mail" label number TB861682250US
Date of Deposit: 22 NOVEMBER 1996
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Linda C. Shelley
Signature of person mailing paper or fee

Respectfully submitted

By Kenneth A. Gandy

Kenneth A. Gandy #33,386
Woodard, Emhardt, Naughton,
Moriarty & McNett
Bank One Center/Tower #3700
Indianapolis, Indiana 46204
United States of America
(317) 634-3456

0704i
Enclosures: Two Appointments of Agent,
Page one of Request
Figs. 1-3 and 5-10

RECEIVED
JUN 23 1997
Woodard, Emhardt, Naughton, Moriarty & McNett

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

From the INTERNATIONAL BUREAU

To:
GANDY, Kenneth, A.
Woodard, Emhardt, Naughton, Moriarty & McNett
Bank One Center/Tower
Suite 3700
111 Monument Circle
Indianapolis, IN 46204
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)	
11 June 1997 (11.06.97)	
Applicant's or agent's file reference	**IMPORTANT INFORMATION**
IU33CIP-3PCT	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US96/15712	30 September 1996 (30.09.96)	29 September 1995 (29.09.95)

Applicant: INDIANA UNIVERSITY FOUNDATION et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :KE,LS,MW,SD,SZ,UG
   EP :AT,BE,CH,DE,DK,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,BR,CA,CN,CZ,HU,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SK,US,VN

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,ML,MR,NE,SN,TD,TG
   National :AL,BA,BB,CU,EE,GE,IS,LC,LK,LR,LT,LV,MG,MK,MX,SG,SI,TR,TT,UA,UZ

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority dat before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of the annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about th applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed until 31 months from the priority date for all States designated f r the purposes of obtaining a European patent including, where applicable, ES which cannot be elected since it is not bound by Chapter II.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No. (41-22) 740.14.35

Authorized officer: Ting Zhao
Telephone No. (41-22) 338.83

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/15712

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A01N 43/04; C12N 15/64, 13/00, 5/00, 1/38, 15/00
US CL :514/44; 435/91.4, 173.4, 240.2, 244; 935/57

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/44; 435/91.4, 173.4, 240.2, 244; 935/57

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Categ ry*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WILLIAMS et al. Umbilical Cord Blood Stem Cells as Targets for Genetic Modification: New Therapeutic Approaches to Somatic Gene Therapy. Blood Cells. 1994, Vol. 20, pages 504-516, especially pages 507-515.	1-10
X	MORITZ et al. Bone Marrow Extracellular Matrix Molecules Improve Gene Transfer into Human Hematopoietic Cells via Retroviral Vectors. Journal of Clinical Investigation. April 1994, Vol. 93, No. 4, pages 1451-1457, especially pages 1452-1457.	1-10
Y	SLUIJS et al. Differential Adherence of Murine Hematopoietic Stem Cell Subsets to Fibronectin. Experimental Hematology. 1994, Vol. 22, pages 1236-1243, especially page 1241,	11-15

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 NOVEMBER 1996	20 NOV 1996

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
DAVE NGUYEN
Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/15712

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim N .
Y	WATT et al. Adhesion Receptors are Differentially Expressed on Developing Thymocytes and Epithelium in Human Thymus. Experimental Hematology. 1992, Vol. 20, pages 1101-1111, especially pages 1109-1110.	11-15
Y	HARAGUCHI, Y, et al. Effects of Polycations on Infection with Human Retroviruses. Int. Conf. AIDS. August 1994, Vol. 10, No. 2, page 114, abstract No. PA0337, see entire abstract.	11-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/15712

B. FIELDS SEARCHED
Electronic data bases consulted (Name f data base and where practicable terms used):

APS, MEDLINE, CATLIT, EMBASE, BIOTECHDS, WPIDS, DISSABS, AIDSLINE
search terms: polybrene, polycation, hematopoietic stem cells, integrin, fibronectin, retroviral vector, transfection, ligand, domain, cell transplantation, grafting, bone marrow